

EXAMPLE 33

Topical KGF-2 in Infected Incisional Wounds

[1050] Bacterial infection of wounds continues to be of great clinical importance. Under normal situations, the complex process of wound healing progresses without difficulty. However, inoculation of a wound by bacteria causes an imbalance of cellular mediators in the inflammatory response resulting in delayed wound healing. Contamination of the open wound inhibits the wound healing process as characterized by decreased wound contraction, lower than normal wound collagen content and decreased tensile strength. Male adult Sprague Dawley rats (n+10/group) were anesthetized with a combination of ketamine (53 mg/kg im) and xylazine (5.3 mg/kg im) on day 1. The dorsal region was shaved and disinfected with 70% alcohol. A full thickness (through the epidermis, dermis to the subcutaneous layer) 2.5 cm surgical wound was created starting approximately 1 cm below the shoulder blades using a sterile no. 10 scalpel. Wounds were coated with 3 equidistant skin staples. The incisions were then inoculated intraincisionally with *Staphylococcus aureus* (107 cfu/ 50 μ l) in PBS. KGF-2 Δ 33 was applied topically at the time of wounding (Day 0) at doses of 0.1, 1 and 10 μ g per wound in a volume of 50 μ l. Wounds were then covered with a gas permeable occlusive dressing (Tegaderm). Animals were sacrificed on day 5 by anesthesia with ketamine/xylazine followed by lethal intracardiac administration of sodium pentobarbital (300 mg/kg). The middle 0.5 cm segment of the wound was excised and snap frozen for collagen determination. Two additional wound strips measuring 0.5 cm in width were excised. Excised wound strips were used for the study of breaking strength using an Instron skin tensiometer. Breaking strength was defined as the greatest force withheld by each wound prior to rupture using and 11 lb load cell at a speed of 0 mm/sec. Two values for each animal were averaged to provide a mean breaking strength value per wound. Statistical analysis was done using an unpaired t test (mean \pm SE).

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[1051] Intrainsisional application of *Staphylococcus aureus* in the wound resulted in a significant impairment in wound healing as measured by breaking strength (noninfected wound treated with bacteria vehicle 136 ± 6 g; infected wound 87 ± 6 g; $p < 0.0001$ in one experiment; noninfected wound treated with bacteria vehicle 200 ± 14 g; infected wound 154 ± 10 g $p = 0.01$ in another experiment). Topical administration of KGF-2 caused an increase in breaking strength which was statistically significant at the 0.1, 1 and 10 μ g doses when compared with the KGF-2 buffer + *S. aureus* control (KGF-2 0.1 μ g 152 ± 16 g ($p = 0.002$); 1 μ g 135 ± 12 g ($p = 0.003$); 10 μ g 158 ± 10 g ($p < 0.0001$) in one experiment; 0.1 μ g 185 ± 10 g ($p = 0.03$); 1 μ g 186 ± 11 g ($p = 0.03$); 10 μ g 190 ± 7 g ($p = 0.009$) in another experiment). Collagen analysis of the middle 0.5 cm wound strip revealed that there was increased collagen content in KGF-2 treated wounds. However, when compared with the buffer controls, a statistically significant increase in collagen content was not observed.

[1052] The studies described in this example test activity in KGF-2 $\Delta 33$ polypeptides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polypeptides, including full length and mature KGF-2, KGF-2 $\Delta 28$, and polypeptide comprising encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polynucleotides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

EXAMPLE 33

Proliferative effect of dosing i.v. every other day with 1 mg/kg of KGF-2 $\Delta 33$

[1053] Male Sprague Dawley rats were intravenously injected with either KGF-2 $\Delta 33$ at a dose of 1 mg/kg, or buffer. The animals were injected either daily or every other day. Each treatment group was injected for one week and sacrificed at the end of the week. On the day of sacrifice, the animals were injected i.p. with 100 mg/kg of BrdU. Two hours later, the animals were sacrificed, and the

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serum was collected. Various tissues were collected and fixed in 10% neutral buffered formalin. The tissues were processed for histological evaluation. The tissues were stained with hematoxylin and eosin, periodic-acid-Schiff, or alcian blue. Additional sections were subjected to immunohistochemical staining with an anti-BrdU antibody. Proliferation was quantitated using an image analysis spectrum, IPlab Spectrum. The serum chemistry analysis was performed using an automated chemistry analyzer. The following parameters were quantitated: thyroid gland weight; proliferation of goblet cells in the small intestine (duodenum, jejunum and ileum); proliferation of goblet cells in the colon; proliferation in the parotid and submandibular glands; and serum chemistry analytes (glucose, BUN, calcium, total protein, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, cholesterol, and triglycerides).

[1054] In the small intestine and colon, daily treatment with KGF-2 caused a significant increase in the number of goblet cells. The every other day treatment did cause a slight increase in the number of goblet cells, however, it did not attain a statistically significant level. In the salivary gland, an increase in cells was observed in the parotid gland only. There was no difference between the treatment groups. There was an enlargement of the thyroid gland due to both dosing regimens. The magnitude of this increase was greater in the daily treatment group. Daily treatment with KGF-2 resulted in statistically significant increase in the following analytes: triglycerides, alkaline phosphatase, calcium, albumin, and total protein. The every other day treatment had no effect on these analytes. Cholesterol levels were elevated in both treatment groups. However, the magnitude of the increase was greater in the daily treatment group. Markers of cellular injury, such as ALT and AST, were similarly reduced in both treatment groups.

[1055] The studies described in this example test activity in KGF-2 $\Delta 33$ polypeptides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polypeptides, including full length and mature KGF-2, KGF-2 $\Delta 28$, and polypeptide comprising encoding amino acids

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77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polynucleotides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

EXAMPLE 34

Formulating a Polypeptide

[1056] The KGF-2 composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the KGF-2 polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

[1057] As a general proposition, the total pharmaceutically effective amount of KGF-2 administered parenterally per dose will be in the range of about 1 $\mu\text{g/kg/day}$ to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, KGF-2 is typically administered at a dose rate of about 1 $\mu\text{g/kg/hour}$ to about 50 $\mu\text{g/kg/hour}$, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

[1058] Pharmaceutical compositions containing KGF-2 are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch); buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of

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administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

[1059] KGF-2 is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., *Biopolymers* 22:547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., *J. Biomed. Mater. Res.* 15:167-277 (1981), and R. Langer, *Chem. Tech.* 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D-(-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped KGF-2 polypeptides. Liposomes containing the KGF-2 are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. USA* 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci. USA* 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

[1060] For parenteral administration, in one embodiment, KGF-2 is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

[1061] Generally, the formulations are prepared by contacting KGF-2 uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the

blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

[1062] The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

[1063] KGF-2 is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

[1064] KGF-2 used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[1065] KGF-2 polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous KGF-2 polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized KGF-2 polypeptide using bacteriostatic Water-for-Injection.

[1066] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, KGF-2 may be employed in conjunction with other therapeutic compounds.

[1067] The compositions of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the compositions of the invention, include but not limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[1068] In one embodiment, the compositions of the invention are administered in combination with other members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the compositions of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), TR6 (International Publication No.

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WO 98/30694), OPG, and neutrokin- α (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

[1069] Conventional nonspecific immunosuppressive agents, that may be administered in combination with the compositions of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

[1070] In a further embodiment, the compositions of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the compositions of the invention include, but are not limited to, tetracycline, metronidazole, amoxicillin, beta-lactamases, aminoglycosides, macrolides, quinolones, fluoroquinolones, cephalosporins, erythromycin, ciprofloxacin, and streptomycin.

[1071] In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the compositions of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome,

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difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap. Also included are corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin), as well as antihistamines,

[1072] In another embodiment, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the compositions of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephalen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

[1073] In an additional embodiment, the compositions of the invention are administered in combination with cytokines. Cytokines that may be administered with the compositions of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha.

[1074] In an additional embodiment, the compositions of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PIGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PIGF-2), as disclosed in Hauser et al., *Growth Factors*, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are incorporated herein by reference herein.

[1075] In an additional embodiment, the compositions of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the compositions of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

[1076] In additional embodiments, the compositions of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

EXAMPLE 35

Method of Treating Decreased Levels of KGF-2

[1077] The present invention also relates to a method for treating an individual in need of an increased level of KGF-2 activity in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of KGF-2 or an agonist thereof.

[1078] Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of KGF-2 in an individual can be treated by administering KGF-2, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of KGF-2 polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of KGF-2 to increase the activity level of KGF-2 in such an individual.

[1079] For example, a patient with decreased levels of KGF-2 polypeptide receives a daily dose 0.1-100 $\mu\text{g/kg}$ of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 24.

EXAMPLE 36

Method of Treating Increased Levels of KGF-2

[1080] The present invention relates to a method for treating an individual in need of a decreased level of KGF-2 activity in the body comprising, administering to such an individual a composition comprising a therapeutically effective amount of KGF-2 antagonist. Preferred antagonists for use in the present invention are KGF-2-specific antibodies.

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- [1081] Antisense technology is used to inhibit production of KGF-2. This technology is one example of a method of decreasing levels of KGF-2 polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.
- [1082] For example, a patient diagnosed with abnormally increased levels of KGF-2 is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 24.

EXAMPLE 37

Method of Treatment Using Gene Therapy - Ex Vivo

- [1083] One method of gene therapy transplants fibroblasts, which are capable of expressing KGF-2 polypeptides, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.
- [1084] At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.
- [1085] pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with

EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

[1086] The cDNA encoding KGF-2 can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector contains properly inserted KGF-2.

[1087] The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the KGF-2 gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the KGF-2 gene (the packaging cells are now referred to as producer cells).

[1088] Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether KGF-2 protein is produced.

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- [1089] The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

EXAMPLE 38

Gene Therapy Using Endogenous KGF-2 Gene

- [1090] Another method of gene therapy according to the present invention involves operably associating the endogenous KGF-2 sequence with a promoter via homologous recombination as described, for example, in U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller *et al.*, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); and Zijlstra *et al.*, *Nature* 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

- [1091] Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous KGF-2, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of KGF-2 so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting

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mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

[1092] In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

[1093] Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous KGF-2 sequence. This results in the expression of KGF-2 in the cell. Expression may be detected by immunological staining, or any other method known in the art.

[1094] Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na₂ HPO₄, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately 3X10⁶ cells/ml. Electroporation should be performed immediately following resuspension.

[1095] Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the KGF-2 locus, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two KGF-2 non-coding sequences are amplified via PCR: one KGF-2 non-coding sequence (KGF-2 fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3' end; the other KGF-2 non-coding sequence (KGF-2

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fragment 2) is amplified with a BamHI site at the 5' end and a HindIII site at the 3' end. The CMV promoter and KGF-2 fragments are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; KGF-2 fragment 1 - XbaI; KGF-2 fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

[1096] Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 $\mu\text{g/ml}$. 0.5 ml of the cell suspension (containing approximately 1.5×10^6 cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 μF and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

[1097] Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37°C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

[1098] The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

EXAMPLE 39

Method of Treatment Using Gene Therapy - In Vivo

- [1099] Advances in gene research have resulted in the development of techniques to deliver and express genes in human cells. The ideal goal for gene therapy is the delivery of normal genes in order to generate active proteins and compensate for the lack of endogenous production (Gorecki, D.C. *et al.*, *Arch. Immunol. Ther. Exp.* 45(5-6):375-381 (1997)).
- [1100] Delivery of genes encoding cytokines or growth factors involved in the different phases of wound healing and tissue repair have the potential to modify the outcome of wound healing (Taub, P.J. *et al.*, *J. Reconst. Microsur.* 14(6):387-390 (1998)). The use of cDNA of growth factors or other cytokines for wound healing and tissue repair has been extensively described (Tchorzewski, M.T. *et al.*, *J. Surg. Res.* 77:99-103(1998)). Genes transferred by a vector can be used to generate new cell lines, identify transplanted cells and express growth factors or enzymes. One of the advantages of gene therapy is to achieve therapeutic concentrations of gene-derived protein locally within the lesion site. Human recombinant KGF-2 protein has been shown to stimulate wound healing of the skin, gastro-intestinal tract and other organ containing cells of epithelial origin. The use of KGF-2 gene is expected to have similar pharmacological profile as the recombinant protein. KGF-2 gene may be involved in events related to tissue repair such as cell proliferation, migration and the formation of extracellular matrix.
- [1101] Transcribed and translated cDNA has been used to deliver genes to sites of interest. Some examples of genes used in this fashion include aFGF, BMP-7 (Breitbart, A.S. *et al.*, *Ann. Plast. Surg.* 24(5):488-495 (1999)). These cells have also been seeded into cell carriers including biodegradable matrices (ex. polyglycolic acid), tissue substitutes or equivalents (ex. artificial skin), artificial organs, collagen-derived matrices, etc. Liposomes have been used to carry

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cDNA. PDGF-BB cDNA in haemagglutinating virus of Japan (HVJ)-liposome suspension was studied in the healing of patellar ligament (Nakamura *et al.*, *Gene Ther.* 5(9):1165-1170 (1998)). Genes can also be delivered directly to the site of action by direct injection (ex. heart).

[1102] Thus, another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) KGF-2 sequences into an animal to increase or decrease the expression of the KGF-2 polypeptide. The KGF-2 polynucleotide may be operatively linked to a promoter or any other genetic elements necessary for the expression of the KGF-2 polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata, H., *et al.*, *Cardiovasc. Res.* 35(3):470-479 (1997), Chao, J., *et al.*, *Pharmacol. Res.* 35(6):517-522 (1997), Wolff, J.A., *Neuromuscul. Disord.* 7(5):314-318 (1997), Schwartz B., *et al.*, *Gene Ther.* 3(5):405-411 (1996), Tsurumi, Y., *et al.*, *Circulation* 94(12):3281-3290 (1996) (incorporated herein by reference).

[1103] The KGF-2 polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The KGF-2 polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[1104] The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the KGF-2 polynucleotides may also be delivered in liposome formulations (such as those taught in Felgner P.L. *et al.*, *Ann. NY Acad. Sci.* 772:126-139 (1995) and

Abdallah B. *et al.*, *Biol. Cell* 85(1):1-7 (1995)) which can be prepared by methods well known to those skilled in the art.

[1105] The KGF-2 polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[1106] The KGF-2 polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *in vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

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[1107] For the naked KGF-2 polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked KGF-2 polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[1108] The dose response effects of injected KGF-2 polynucleotide in muscle *in vivo* is determined as follows. Suitable KGF-2 template DNA for production of mRNA coding for KGF-2 polypeptide is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

[1109] Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The KGF-2 template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

- [1110] After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 μ m cross-section of the individual quadriceps muscles is histochemically stained for KGF-2 protein expression. A time course for KGF-2 protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of KGF-2 DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using KGF-2 naked DNA.

EXAMPLE 40

KGF-2 Therapy for Inflammatory Bowel Disease

- [1111] In this example, the inhibition of pathologic changes in colons of mice caused by exposure to dextran sodium sulfate (DSS) in drinking water by systemic (intranasal) and intraperitoneal administration of KGF-2 polynucleotides is determined.
- [1112] Intranasal administration. A polynucleotide encoding KGF-2 Δ 33 is introduced into the nasal passages of anaesthetized female Swiss Webster mice (n=10/group) through a blunted 26 gauge needle at a dosage of 1, 10 or 100 μ g of polynucleotide. Control polynucleotide is administered to a separate group of mice. Five days after intranasal administration of the polynucleotide, 5% DSS is added to the drinking water. Mice are monitored for body weight, hematocrit, and stool score. After seven days of exposure to DSS in the drinking water, mice are sacrificed. Histopathologic assessment of colon and small intestine is performed. RT-PCR analysis is performed to determine expression of KGF-2 in liver, spleen and colon.

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[1113] Intraperitoneal administration. A polynucleotide encoding KGF-2 Δ 33 is injected intraperitoneally into female Swiss Webster mice (n=10/group) through a blunted 26 gauge needle at a dosage of 1, 10 or 100 μ g of polynucleotide on days 0 and 3. Control polynucleotide is administered to a separate group of mice using an identical regimen. On day 7, 5% DSS is added to the drinking water. Mice are monitored for body weight, hematocrit, and stool score. On day 14, mice are sacrificed. Histopathologic assessment of colon and small intestine is performed. RT-PCR analysis is performed to determine expression of KGF-2 in liver, diaphragm and colon.

[1114] The studies described in this example test activity in KGF-2 Δ 33 polynucleotides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polynucleotides, including full length and mature KGF-2, KGF-2 Δ 28, and polynucleotides encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polypeptides, variants, fragments, agonists, and/or antagonists; and any KGF-2 mutant described herein.

EXAMPLE 41

KGF-2 Therapy for Ocular Surface Disease

[1115] In this example, the effect of subconjunctival administration of Δ 33 KGF-2 polynucleotides on the conjunctiva, cornea or lacrimal gland of rats is determined.

[1116] A polynucleotide encoding Δ 33 KGF-2 is injected into the subconjunctival space of anaesthetized Female Sprague Dawley rats (150-200 g body weight, 6/treatment group) at a dosage of 1, 10 or 100 μ g. Control polynucleotide is injected in a similar fashion to a separate group of control rats. Separate groups of rats are sacrificed at 3, 7 and 14 days post injection. BrdU is administered intraperitoneally to some of the rats 30 minutes before euthanasia.

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The eye and surrounding tissues are removed for histologic analysis. The extent of BrdU incorporation in the epithelial cells of the cornea, conjunctiva and lacrimal glands is measured. The thickness of the epithelial layer in the cornea and conjunctiva is assessed. The number of goblet cells in the conjunctiva is measured.

- [1117] The studies described in this example test activity in KGF-2 $\Delta 33$ polynucleotides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polynucleotides, including full length and mature KGF-2, KGF-2 $\Delta 28$, and polynucleotides encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polypeptides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

EXAMPLE 42

KGF-2 Therapy for Salivary Gland Dysfunction

- [1118] In this example, the effect of KGF-2 polynucleotide administration into the papillae of the parotid salivary gland duct of normal rats on the epithelial cells of the ducts and acini of that gland is determined.
- [1119] Female Sprague Dawley Rats (150-250 grams, 6/group) are anesthetized by the intramuscular injection of ketamine and xylazine. A polynucleotide encoding $\Delta 33$ KGF-2 is introduced into the papilla of the parotid salivary gland using a 30 gauge steel gavage needle, at a dosage of 1, 10 or 100 μ g. The polynucleotide is infused over a ten minute period at a rate of 1 μ l per minute. Control polynucleotide is administered to a separate group of rats. Separate groups of rats are sacrificed at 3, 7 and 14 days after infusion. BrdU is administered intraperitoneally 30 minutes before euthanasia. The salivary glands are weighed, and the number of BrdU-staining cells is counted on histologic

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section. In a separate experiment, pilocarpine-stimulated saliva secretion is measured in rats at 7 days after infusion.

- [1120] The studies described in this example test activity in KGF-2 $\Delta 33$ polynucleotides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polynucleotides, including full length and mature KGF-2, KGF-2 $\Delta 28$, and polynucleotides encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polypeptides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

EXAMPLE 43

KGF-2 Therapy for Dermal Wound Healing

- [1121] In this example, the ability of KGF-2 polynucleotide to stimulate wound healing in the normal rat and diabetic mice is determined.
- [1122] Normal rat. Anesthetized female Sprague Dawley rats (175-250 gm 6/treatment group) are wounded with 8 mm biopsy punches. $\Delta 33$ KGF-2 polynucleotide (1, 10 or 30 μ g) is delivered intradermally at 4 different sites along the wound. Control polynucleotide is administered in a similar manner to a separate group of rats. The wounds are covered with sterile ventilated fabric pads. After the pad is positioned, waterproof adhesive tape is wrapped around the midsection of the rat. Separate groups of rats are sacrificed at 2 and 5 days post wounding. The wound tissues are fixed in 10% formalin embedded in paraffin. BrdU incorporation in proliferating epithelial cells in pre-existing and new epidermis; and the length and thickness of the new epithelial tongue is measured.
- [1123] Diabetic mice. Diabetic mice (db+/db+, 10/treatment group) and nondiabetic mice (db+/m+, 10/treatment group) are wounded with a 6 mm punch wound in the dorsum. $\Delta 33$ KGF-2 polynucleotide (1, 10 or 30 μ g) is delivered intradermally at 4 different sites along the wound. Control polynucleotide is

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administered in a similar manner to a separate group of mice. The wounds are covered with Tegaderm (diabetic mice) or Tegaderm plus adhesive tape (nondiabetic mice). The wounds are photographed on days 0, 3, 7, 10 and 14 post wounding. The surface area of the wounds are measured by image analysis.

- [1124] The studies described in this example test activity in KGF-2 $\Delta 33$ polynucleotides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polynucleotides, including full length and mature KGF-2, KGF-2 $\Delta 28$, and polynucleotides encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polypeptides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

EXAMPLE 44

Constructs for KGF-2 delivery

- [1125] An appropriate construct for KGF-2 gene therapy delivery is pVGI.0-KGF-2. This construct contains the full native open reading frame of KGF-2 cloned into the expression vector pVGI.0. pVGI.0 contains a kanamycin resistance gene, a CMV enhancer, and an RSV promoter. pVGI.0-KGF-2 was deposited at the American Type Culture Collection Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209, on June 30, 1999, and given ATCC Deposit No. PTA290. This construct was made by subcloning the KGF-2 ORF from a previously sequence verified KGF-2 construct into the expression vector pVGI.0, using methods well known in the art.

- [1126] Another appropriate construct for KGF-2 delivery is pVGI.0-MPIFspKGF2 $\Delta 33$. This construct contains the native sequence of KGF-2 $\Delta 33$ fused to the MPIF (CK68) heterologous signal peptide cloned into the expression vector pVGI.0. pVGI.0-MPIFspKGF2 $\Delta 33$ was deposited at the American Type Culture Collection Patent Depository, 10801 University Boulevard, Manassas,

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VA 20110-2209, on June 30, 1999, and given ATCC Deposit No. PTA289. This construct was made using methods well known in the art and the following primers:

5' primer:

GAGCGCGGATCCGCCACCATGAAGGTCTCCGTGGCTGCCCTCTCC
TGCCTCATGCTTGTTACTGCCCTTGGATCTCAGGCCAGCTACAATCA
CCTTCAAGGAGATG (SEQ ID NO:149)

3' primer: GAGCGC GGATCC CTATGAGTGTACCACCATTGGAAG
(SEQ ID NO:150)

EXAMPLE 45

Angiogenesis During KGF-2 Gene Therapy

[1127] Characterization of the multiple aspects of microvascular physiology in transparent window systems in mice have provided valuable data on angiogenesis, inflammation, microvascular transport, tissue rejection and tumor physiology. In this example, the development of vasculature during a wound healing response in implanted collagen gels is assessed through direct observation of the tissue and associated microvascular bed through an implanted skin window. This model is used to determine if KGF-2 gene therapy can simultaneously induce an accelerated tissue regrowth and revascularization.

[1128] Skin biopsies from nude mice are digested in collagenase, the resulting cell suspensions washed and then cultured in DMEM with 10% FBS to obtain dermal fibroblasts. Confluent fibroblast cultures are transfected with KGF-2 or control polynucleotide then collected and washed in PBS. 10⁶ cells are suspended in 20 μ l of collagen matrix. Samples of cell suspension are removed for Western blot confirmation of KGF-2 production. A 2 mm punch biopsy is made into an existing dorsal skin window and the skin sandwiched between two glass coverslips. The cell collagen mixture is placed into the circular wound and

the chamber sealed. The implanted gels are observed at regular intervals for vessel development. Tissue regrowth into the wound is monitored as changes in the optical density of the collagen gel over a three week period. Tissue from the dorsal chambers is removed following the conclusion of the study for histological evaluation. Control experiments involve the addition of KGF-2 polypeptide or buffer into collagen gels in place of fibroblasts.

[1129] Mouse preparation. The surgical procedures are performed in Swiss nude mice. For the surgical procedures, animals (20-30 g) are anesthetized with s.c. injection of a cocktail of 90 mg Ketamine and 9 mg Xylazine per kg body weight. All surgical procedures are performed under aseptic conditions in a horizontal laminar flow hood, with all equipment being steam, gas or chemically sterilized. During surgery, the body temperature of the animals is kept constant by means of a heated work surface. All mice are housed individually in microisolator cages and all manipulations are done in laminar flow hoods. Buprenorphine (0.1 mg/kg q 12h) is administered as an analgesic for 3 days post implantation.

[1130] Mice are positioned such that the chamber is sandwiched between a double layer of skin that extends above the dorsal surface. One layer of skin is removed in a circular area ~15 mm in diameter. The second layer (consisting of epidermis, fascia, and striated muscle) is positioned on the frame of the chamber and covered with a sterile glass coverslip. The chamber is held in place with nylon posts which pass through the extended skin and holes along the top of the chamber. After 3 days, the coverslip is carefully removed and the gel inserted. A new, sterile coverslip is then placed on the viewing surface. Measurements are made by morphometric analysis using an Intensified CCD camera, S-VHS videocassette recorder and direct digital image acquisition. Mice with implanted changers were observed for 28 days.

[1131] Measurements. Mice are anesthetized with s.c. injection of a cocktail of 90 mg Ketamine and 9 mg Xylazine per kg body weight, then positioned on a sterile plastic stage assembly. Vascular maps of the window are made using transillumination (dorsal skin window) or following an injection of 100 μ l of

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BSA-FITC (1 mg/ml, i.v.) and epi-illumination. Video recordings of vascular beds are made at a range of magnifications (from 1X to 40X) as well as digital frames for off-line analysis. Angiogenesis determinations of implanted gels are made from offline analysis of video tapes.

- [1132] The studies described in this example test activity in KGF-2 $\Delta 33$ polynucleotides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polynucleotides, including full length and mature KGF-2, KGF-2 $\Delta 28$, and polynucleotides encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polypeptides, variants, fragments, agonists, and/or antagonists; as well as any of the KGF-2 mutants described herein.

EXAMPLE 46

KGF-2 Transgenic Animals

- [1133] The KGF-2 polypeptides can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e.g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

- [1134] Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., *Appl. Microbiol. Biotechnol.* 40:691-698 (1994); Carver et al., *Biotechnology (NY)* 11:1263-1270 (1993); Wright et al., *Biotechnology (NY)* 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al.,

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Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson *et al.*, *Cell* 56:313-321 (1989)); electroporation of cells or embryos (Lo, *Mol. Cell. Biol.* 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer *et al.*, *Science* 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitano *et al.*, *Cell* 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," *Intl. Rev. Cytol.* 115:171-229 (1989), which is incorporated by reference herein in its entirety.

[1135] Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campbell *et al.*, *Nature* 380:64-66 (1996); Wilmut *et al.*, *Nature* 385:810-813 (1997)).

[1136] The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, i.e., mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, e.g., head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko *et al.* (Lasko *et al.*, *Proc. Natl. Acad. Sci. USA* 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred.

[1137] Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal

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sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu *et al.* (Gu *et al.*, *Science* 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. The contents of each of the documents recited in this paragraph is herein incorporated by reference in its entirety.

[1138] Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, in situ hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

[1139] Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

- [1140] Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of KGF-2 polypeptides, studying conditions and/or disorders associated with aberrant KGF-2 expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

EXAMPLE 47

KGF-2 Knock-Out Animals

- [1141] Endogenous KGF-2 gene expression can also be reduced by inactivating or "knocking out" the KGF-2 gene and/or its promoter using targeted homologous recombination. (E.g., see Smithies *et al.*, *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson *et al.*, *Cell* 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e.g., see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

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[1142] In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the KGF-2 polypeptides. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

[1143] Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

[1144] When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while

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allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

- [1145] Knock-out animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of KGF-2 polypeptides, studying conditions and/or disorders associated with aberrant KGF-2 expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

EXAMPLE 48

Construction of KGF-2 mutants

- [1146] To create point mutants, the indicated primers were used in PCR reactions using standard conditions well known to those skilled in the art. The resulting products were restricted with either Nde and Asp718 and cloned into pHE4; or with BamHI and Xba and cloned into pcDNA3; as indicated. Any of the described KGF-2 variants can be produced in other vectors, or by themselves, using methods well known in the art.

pHE4:KGF2:R80-S208 was constructed using following primers:

5' primer: CCGGC CATATG CGTAAACTGTTCTCTTTCACC (SEQ ID NO:151)

3' primer: CCGGC GGTACC TTATTATGAGTGTACCACCATTGG (SEQ ID NO:152)

pHE4:KGF2:A63-S208(R68G) was constructed using following primers:

5' primer: GATCGC CATATG GCTGGTCGTCACGTTCGTTTC (SEQ ID NO:153)

3' primer: GATCGC GGTACC TTATTATGAGTGTACCACCATTGGAAG (SEQ ID NO:154)

pHE4:KGF2:A63-S208(R68S) was constructed using following primers:

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5' primer: GATCGC CATATG GCTGGTCGTCACGTTTCGTTTC (SEQ ID NO:155)

3' primer: GATCGC GGTACC TTATTATGAGTGTACCACCATTGGAAG (SEQ ID NO:156)

pHE4:KGF2:A63-S208(R68A) was constructed using following primers:

5' primer: GATCGC CATATG GCTGGTCGTCACGTTTCGTTTC (SEQ ID NO:157)

3' primer: GATCGC GGTACC TTATTATGAGTGTACCACCATTGGAAG (SEQ ID NO:158)

pHE4:KGF2:A63-S208(R78R80K81A) was constructed using following primers:

5' primer: GATCGC CATATG GCTGGTCGTCACGTTTCGTTTC (SEQ ID NO:159)

3' primer: GATCGC GGTACC TTATTATGAGTGTACCACCATTGGAAG (SEQ ID NO:160)

pcDNA3:KGF2(K136137139144A) was constructed using following primers:

5' primer:

GATCGCGGATCCGCCACCATGTGGAAATGGATACTGACACATTGTG C (SEQ ID NO:161)

3' primer: GATCGCTCTAGATTATGAGTGTACCACCATTGGAAGAAAG (SEQ ID NO:162)

pcDNA3:KGF2(K151153R155A) was constructed using following primers:

5' primer:

GATCGCGGATCCGCCACCATGTGGAAATGGATACTGACACATTGTG C (SEQ ID NO:163)

3' primer: GATCGCTCTAGATTATGAGTGTACCACCATTGGAAGAAAG (SEQ ID NO:164)

pcDNA3:KGF2(R174K183A) was constructed using following primers:

5' primer:

GATCGCGGATCCGCCACCATGTGGAAATGGATACTGACACATTGTG C (SEQ ID NO:165)

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3' primer: GATCGCTCTAGATTATGAGTGTACCACCATTGGAAGAAAG
(SEQ ID NO:166)

pcDNA3:KGF2(R187R188A) was constructed using following primers:

5' primer:

GATCGCGGATCCGCCACCATGTGGAAATGGATACTGACACATTGTG
C (SEQ ID NO:167)

3' primer: GATCGCTCTAGATTATGAGTGTACCACCATTGGAAGAAAG
(SEQ ID NO:168)

pHE4:KGF2.A63(K136137139144A) was constructed using the following
primers:

5' primer: GATCGCCATATGGCTGGTCGTCACGTTCGTTC (SEQ ID
NO:169)

3' primer: GATCGCGGTACCTTATTATGAGTGTACCACCATTGGAAG
(SEQ ID NO:170)

pHE4:KGF2.A63(K151153R155A) was constructed using the following
primers:

5' primer: GATCGCCATATGGCTGGTCGTCACGTTCGTTC (SEQ ID
NO:171)

3' primer: GATCGCGGTACCTTATTATGAGTGTACCACCATTGGAAG
(SEQ ID NO:172)

EXAMPLE 49

Use of KGF-2 for Treating and/or Preventing Infertility

[1147] Implantation is the single most critical factor in a successful pregnancy and is clinically and economically important. In humans, the greatest fraction of the 70% loss in embryonic life occurs at implantation. The mouse is the model of choice for studying mammalian implantation. Three essential cell lineages differentiate and divide in the peri-implantation mouse embryo: embryonic,

placental and yolk sac precursors. Fibroblast growth factor (FGF)-4 is essential for development of all three cell lineages.

[1148] It has been found, using a 'transient transgenic' approach to deliver gain-of-function and loss-of-function (dominant negative) FGF receptor genes, that endogenous FGF signaling is necessary for cell division of all stem cells for the embryo and placenta lineages in the mouse embryo starting at the fifth cell division two days before implantation.

[1149] Interestingly, it has been found that null mutant for *fgfr-2* and *fgf4* die in uteri within a day after implantation and the ICM dies. Before the embryo implants into the uterus cells in the embryonic lineage and in the placental lineage require FGF to continue proliferating.

[1150] It is possible that one or several of the other 19 FGF ligand is expressed transiently in the mouse preimplantation embryo and this ligand delays the effect of the *fgfr-2* and *fgf4* null mutants until after implantation. We have tested for six FGF ligand using RT-PCR. To date, KGF-2 and FGF-8 are the only FGF ligands, besides FGF-4, detected in the preimplantation embryo. KGF-2 mRNA is detected in the embryo after the two cell stage and through early post-implantation.

[1151] *KGF-2* null mutants suggest that KGF-2 is not essential for survival during the expression of KGF-2 in peri-implantation mouse embryos (Min et al., 1998; Sekine et al., 1999). However, other FGF family members may compensate or be redundant for KGF-2 during peri-implantation embryonic development. Many redundant genetic effects have been observed during analysis of null mutants in mice and compensation within a gene family has also been observed (Thomas et al., 1995; Stein et al., 1994). KGF-2 may be more important in early development than is suggested by the *KGF-2* null mutants.

[1152] The best way to detect whether KGF-2 may have role in early development at a time when the null mutants suggest no essential function, is to do gain-of-function experiments. These experiments test whether KGF-2 has an influence on growth of perimplantation embryos (Rappolee et al., 1994), on the

placental/trophoblast cells in blastocyst outgrowths (Chai et al., 1998) and in endoderm lineage cells in inner cell mass (ICM) outgrowths (Rappolee et al., 1994). Loss-of-function tests can be done in a limited way by use of antisense oligonucleotides (Rappolee et al., 1992) or blocking antibodies (LaFleur et al., 1996). It is known that the embryos undergo size regulation, large positive and negative changes in cell number are homeostatically regulated, soon after implantation (Rappolee, 1998). This suggests that small, sublethal KGF-2-dependent effects might be totally missed in the *KGF-2* null mutants. Loss- and gain-of-function experiments are used to test peri-implantation mouse embryos for the effects of KGF-2.

[1153] To date, the detection of mRNA for a growth factor in the preimplantation mouse embryo has universally led to detection of the corresponding protein. (Rappolee et al., 1998, 1992, 1994; reviewed in Rappolee 1998, 1999). To determine whether KGF-2 protein is present (and where) in embryos where KGF-2 mRNA was detected, an antibody to KGF-2 suitable for immunocytochemistry is used.

[1154] One skilled in the art could easily modify the exemplified studies to test the activity of any KGF-2 polypeptide, including full length and mature KGF-2, KGF-2 $\Delta 28$, KGF-2 $\Delta 33$, and polynucleotides encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polynucleotides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

EXAMPLE 50

Detection of KGF-2 in a clinical sample

[1155] Purified Goat PAb is diluted to 2 $\mu\text{g/ml}$ in the coating buffer (0.05 M NaHCO_3 , pH 9.5). 100 μl diluted antibody is added per well to an Immuno 4 microplate. The microplate is stored overnight at 4°C. The antibody solution is

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decanted from the plate. 200 μ l of blocking buffer (1% dry milk (BioRad) in coating buffer) is added to each well. The plate is allowed to incubate at room temperature for 2 hours. The blocking buffer is decanted from the plate. The plate is vacuum aspirated and allowed to dry completely in a vacuum chamber at 32°C for 1.5 hours. The plate is removed from the vacuum chamber and sealed in a mylar pouch with 3 desiccant packs. The plate is stored at 4°C until ready to be used.

[1156] KGF-2 is diluted to 16 ng/ml with diluent 1 (0.1% Tween 20, 1xPBS, 1% BSA, and 0.001% Thimerosal), then a subsequent 2.5x dilution is made for the next 7 dilutions. The concentration range from 16 ng/ml to 0.026 ng/ml is used as the standard. The background wells consist of diluent without protein.

[1157] The unknown samples are diluted 10X, 50X, and 250X with diluent 1. 100 μ l per well of the serial diluted standard solution and the unknown samples are added to the coated ELISA plate. The plate is stored at 4°C overnight. The solutions are decanted from the plate. The plate is washed with washing buffer (0.1% Tween 20 and 1x PBS) five times, using the Wheaton Instrument set at 1.6 ml (each well receives 200 μ l per wash). 15 seconds of incubation of washing buffer is allowed between each wash.

[1158] The detector, biotinylated chicken anti-KGF-2 is diluted to 0.5 μ g/ml in diluent 1. 100 μ l of the diluted detector is added to each well. The plate is incubated for 2 hours at room temperature. The solution is decanted and the plate is washed with washing buffer 5 times, as before. 15 seconds of incubation time is allowed between each wash.

[1159] Peroxidase streptavidin is diluted to 1:2000 in diluent 1. 100 μ l per well of the diluted peroxidase streptavidin is added to the plate and allowed to incubate at room temperature for 1 hour. The plate is decanted and washed with washing buffer five times. 15 seconds of incubation of washing buffer is allowed between each wash. The plate is not allowed to dry.

[1160] Equal amounts of room temperature TMB peroxidase substrate and the peroxidase solution B (from the TMB Peroxidase Microwell Substrate System,

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KPL) are mixed. 100 μ l of the mixed solution is added to each well and the color is allowed to develop at room temperature for 10 minutes. The color development is stopped by adding 50 μ l of 1M H₂SO₄ to each well. The plate is read at 450 nm.

EXAMPLE 51

Construction of E. coli optimized truncated KGF-2

[1161] In order to increase expression levels of a truncated KGF-2 in an E. coli expression system, the codons of the gene were optimized to highly used E. coli codons.

[1162] For example, the following construct, termed pHE4:KGF-2.A63-S608, was made.

5' CATATGGCTGGTCGTCACGTTCTTACAACCACCTGCAGGGT
GACGTTCTGTTGGCGTAAACTGTTCTCTTTACCAAATACTTCCTGAA
AATCGAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTG
CCCGTACAGCATCCTGGAGATAACATCAGTAGAAATCGGAGTTGTT
GCCGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGA
AGGGGAAACTCTATGGCTCAAAAGAATTTAACAATGACTGTAAGCT
GAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATCATT
TAACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTGAATGG
AAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGGAAAAACA
CCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAATAAGGTACC
3' (SEQ ID NO:173)

[1163] A plasmid comprising a cDNA having the nucleotide sequence of SEQ ID NO:173 was deposited as ATCC Deposit No. PTA-2183 on July 3, 2000, at the American Type Culture Collection, Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209.

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[1164] Another construct, termed pHE4:KGF-2.A63-S208 cod.opt, was constructed using the following primers:

sense 5' GACTACATATGGCTGGTCGTCACGTTTCGTTCTTACAACC
ACCTGCA GG3' (SEQ ID NO:174)

antisense 5' CTAGTCTCTAGATTATTATGAGTGTACAACCATCG
GCAGGAAGTGAG 3' (SEQ ID NO:175)

[1165] The nucleotide sequence of the pHE4:KGF-2.A63-208 cod.opt is as follows:

5' ATGGCTGGTCGTCACGTTTCGTTCTTACAACCACCTGCAGGGTG
ACGTTTCGTTGGCGTAAACTGTTCTCTTTACCAAATACTTCCTGAAA
ATCGAAAAGAACGGTAAAGTTTCTGGTACCAAGAAAGAAAAGTGC
CCGTACTCTATCCTGGAAATCACCTCCGTTGAAATCGGTGTTGTAG
CCGTTAAAGCCATCAACTCCAACCTATTACCTGGCCATGAACAAAAA
GGGTAAACTGTACGGCTCTAAAGAATTCAACAACGACTGCAAACT
GAAAGAACGTATCGAAGAGAACGGTTACAACACCTACGCATCCTT
CAACTGGCAGCACAACGGTCGTCAGATGTACGTTGCACTGAACGGT
AAAGGCGCTCCGCGTCGCGGTCAGAAAACCCGTCGCAAAAACACC
TCTGCTCACTTCCTGCCGATGGTTGTACACTCATAATAA 3' (SEQ ID
NO:176)

[1166] A plasmid comprising a cDNA having the nucleotide sequence of SEQ ID NO:176 was deposited as ATCC Deposit No. PTA-2184 on July 3, 2000, at the American Type Culture Collection, Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209.

[1167] Both constructs described in this example are useful in the production of KGF-2 polypeptides, for example, as described in Example 13. Nucleotides 4 to 444 of SEQ ID NO:173 and nucleotides 1 to 441 of SEQ ID NO:176 encode amino acids 63 to 208 of SEQ ID NO:2, plus an N-terminal methionine.

EXAMPLE 52

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Stimulation of pulmonary epithelial cells

[1168] Rats receiving an intratracheal dose of KGF-2 Δ 28 were injected with BrdU hours later, and BrdU⁺ alveolar cells quantified. A single IT infusion at a dose of 0.1, 0.3 or 1 mg/kg induced a significant 10-fold increase in the number of BrdU⁺ cells per microscopic field compared to controls. Histologic evaluation of H & E stained sections revealed no fibrosis, but showed alveolar hyperplasia characterized by the "knobby proliferation" associated with Type II pneumocyte cell division. In a monkey study, following administration of 1 mg/kg IT KGF-2 Δ 28, the number of BrdU positive alveolar cells was significantly increased over controls (65 BrdU⁺ cells/field v. 4). In addition, bronchial epithelial cells exhibited a robust proliferative response following infusion of KGF-2 Δ 28.

[1169] The studies described in this example test activity in KGF-2 Δ 28 polypeptides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polypeptides, including full length and mature KGF-2, KGF-2 Δ 33, and polypeptide comprising amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polynucleotides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

[1170]

EXAMPLE 53

Prophylactic treatment of mucositis

[1171] KGF-2 Δ 33 was shown to be protective in studies involving radiation-induced mortality in mice, cyclophosphamide-induced bladder mucositis in rats, indomethacin-induced intestinal mucositis in rats and LPS-induced endotoxemia in mice. Pretreatment of mice with 1 mg/kg, intravenously of KGF-2 Δ 33 for 3 days prior to exposure to a lethal split dose of whole body irradiation significantly

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($p < 0.03$) reduced mortality compared to the control group (30% vs 90% mortality). In experimental cyclophosphamide-induced cystitis, a single IV dose of KGF-2 Δ 33 (1 mg/kg), injected 24 hours before cyclophosphamide, significantly ($p < 0.05$) lowered cyclophosphamide-induced bladder wet weight, a surrogate marker of edema, 73%. Based on histologic evaluation of edema, hemorrhage, inflammation and ulceration, KGF-2 Δ 33 treatment reduced the histologic score to 2.2 compared with 7.3 for the control group. In acute indomethacin-induced intestinal injury, one IV injection of KGF-2 Δ 33 (1 mg/kg) 3 days before initiation of treatment with indomethacin, significantly ($p < 0.05$) reduced indomethacin-mediated pathology 36-49%, as measured by the reduction of intestinal ulceration, inflammatory score and edema. In a murine model of sub-lethal endotoxic shock, KGF-2 Δ 33 (10 mg/kg, IP) administered 10 minutes prior to LPS injection, significantly ($p < 0.001$) reduced elevated levels of serum TNF from a control value of 7600 pg/ml to 1400 pg/ml, and lowered serum IL-1 and IL-6 levels almost 50%. KGF-2 Δ 33 can thus be used to treat mucositis in patients undergoing cancer chemo- or radio-therapy.

[1172] The studies described in this example test activity in KGF-2 Δ 33 polypeptides. However, one skilled in the art could easily modify the exemplified studies to test the activity of other KGF-2 polypeptides, including full length and mature KGF-2, KGF-2 Δ 28, and polypeptide comprising encoding amino acids 77 to 208, 80 to 208, and 93 to 208 of KGF-2; and KGF-2 polynucleotides, variants, fragments, agonists, and/or antagonists; as well as any KGF-2 mutant described herein.

[1173] It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples.

[1174] Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, within the scope of the appended claims, the invention may be practiced otherwise than as particularly described.

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[1175] The entire disclosure of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference.

Applicant's or agent's file reference number	1488.036PC0P	International application No. (TO BE ASSIGNED)
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A. The indications made below relate to the deposited microorganism or other biological material referred to in the description on page <u>4</u> , line <u>11</u> .	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit December 16, 1994	Accession Number 75977
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
DNA Plasmid, 366885A	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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Applicant's or agent's file reference number	1488.036PC0P	International application No. (TO BE ASSIGNED)
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B. IDENTIFICATION OF DEPOSIT	
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Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit September 29, 1994	Accession Number 75901
C. ADDITIONAL INDICATIONS (leave blank if not applicable)	
This information is continued on an additional sheet <input type="checkbox"/>	
DNA Plasmid, 366,885	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
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B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit January 9, 1998	Accession Number 209575
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
DNA Plasmid pHEKGF-2delta33	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit June 30, 1999	Accession Number PTA-290
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
DNA Plasmid pVGI-0: KGF2 (F.L.) (Ref. PF155)	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit June 30, 1999	Accession Number PTA-289
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
DNA Plasmid pVGI-0:Δ33 KGF2 (Ref. PF155)	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
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B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 03 July 2000	Accession Number PTA-2183
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
(DNA Plasmid (Human): pHE4.KGF-2.A63-S208)	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
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B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
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Date of deposit 03 July 2000	Accession Number PTA-2184
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
(DNA Plasmid (Human): pHE4.KGF-2.A63-S208c.o.)	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
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WHAT IS CLAIMED IS:

1. A method for treating inflammation comprising administering to a patient in need thereof a therapeutically effective amount of KGF-2Δ28.
2. The method of claim 1, wherein said KGF-2Δ28 is administered via gene therapy.
3. A method of stimulating the growth of pulmonary epithelial cells, comprising contacting said cells with KGF-2Δ28.
4. The method of claim 3, wherein said cells comprise an isolated polynucleotide encoding KGF-2Δ28.
5. A method of preventing mucositis, comprising administered to an individual a prophylactically effective amount of KGF-2Δ33.

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1 ATGTGGAAATGGATACTGACACATTGTGCCTCAGCCTTTCCCCACCTGCCCGGCTGCTGC 60
-----+-----+-----+-----+-----+-----+
TACACCTTTACCTATGACTGTGTAACACGGAGTCGGAAGGGGTGGACGGGCCGACGACG
M W K W I L T H C A S A F P H L P G C C

61 TGCTGCTGCTTTTTGTTGCTGTTCTTGGTGTCTCCGTCCCTGTCACCTGCCAAGCCCTT 120
-----+-----+-----+-----+-----+-----+
ACGACGACGAAAAACAACGACAAGAACCACAGAAGGCAGGGACAGTGGACGGTTCCGGAA
C C C F L L L F L V S S V P V T C Q A L

121 GGTCAGGACATGGTGTCAACAGAGGCCACCAACTCTTCTCCTCCTCCTTCTCCTCTCCT 180
-----+-----+-----+-----+-----+-----+
CCAGTCCTGTACCACAGTGGTCTCCGGTGGTTGAGAAGAAGGAGGAGGAAGAGGAGAGGA
G Q D M V S P E A T N S S S S S F S S P

181 TCCAGCGCGGGAAGGCATGTgCGGAGCTACAATCACCTTCAAGGAGATGTCCGCTGGAGA 240
-----+-----+-----+-----+-----+-----+
AGGTCGCGCCCTTCCGTACAcGCCTCGATGTTAGTGGAAGTTCCTCTACAGGCGACCTCT
S S A G R H V R S Y N H L Q G D V R W R

MATCH WITH FIG. 1B

FIG.1A

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MATCH WITH FIG. 1A

241 AAGCTATTCTCTTTCACCAAGTACTTTCTCAAGATTGAGAAGAACGGGAAGGTCAGCGGG 300
-----+-----+-----+-----+-----+-----+
TTCGATAAGAGAAAGTGGTTCATGAAAGAGTTCTAACTCTTCTTGCCCTTCCAGTCGCCC
K L F S F T K Y F L K I E K N G K V S G
301 ACCAAGAAGGAGAACTGCCCCGTACAGCATCCTGGAGATAACATCAGTAGAAATCGGAGTT 360
-----+-----+-----+-----+-----+-----+
TGGTTCTTCCTCTTGACGGGCATGTCGTAGGACCTCTATTGTAGTCATCTTTAGCCTCAA
T K K E N C P Y S I L E I T S V E I G V
361 GTTGCCGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGAAGGGGAAACTC 420
-----+-----+-----+-----+-----+-----+
CAACGGCAGTTTCGGTAATTGTCGTTGATAATGAATCGGTACTTGTTCTTCCCCTTTGAG
V A V K A I N S N Y Y L A M N K K G K L
421 TATGGCTCAAAAGAATTTAACAATGACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGA 480
-----+-----+-----+-----+-----+-----+
ATACCGAGTTTTCTTAAATTGTTACTGACATTCGACTTCCTCTCCTATCTCCTTTTACCT
Y G S K E F N N D C K L K E R I E E N G

MATCH WITH FIG. 1C

FIG.1B

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MATCH WITH FIG. 1B

```

481  TACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTG
      -----+-----+-----+-----+-----+-----+
      ATGTTATGGATACGTAGTAAATTGACCGTCGTATTACCCTCCGTTTACATACACCGTAAC
      Y N T Y A S F N W Q H N G R Q M Y V A L
      AATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGGAAAAACACCTCTGCTCAC
541  -----+-----+-----+-----+-----+-----+
      TTACCTTTTCCTCGAGGTTCCCTCTCCTGTCTTTGTGCTTCCTTTTGTGGAGACGAGTG
      N G K G A P R R G Q K T R R K N T S A H
      TTTCTTCCAATGGTGGTACACTCATAG
601  -----+-----+-----+-----+-----+
      AAAGAAGGTTACCACCATGTGAGTATC
      F L P M V V H S *
```

FIG.1C

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	1					50
FGF4	MS.GPGTAAV	ALLPAVLLAL	LA.....	.PWAGRGGAA	APTAPNGTLE	
FGF6	MSRGAGRLQG	TLWALVFLGI	LV.....	.GMVVPSPAG	TR.ANNTLLD	
FGF5MSL	SFLLLLFFSH	LILSAWAHGE	KRLAPKGQPG	PAATDRNPIG	
FGF1	
FGF2	
FGF9MAPLGEVG	NYFGVQDAVP	
FGF7MHKW	ILTWILPTLLYRSCF	HIICLVGTIS	
KGF2MWKW	ILTHCASAFP	HLPGCCCCCF	LLLFLVSSVP	
FGF3MGL	IWLLLLSLLE	
FGF8	MGSPRSALSC	LLLHLLVLCL	QAQVRSAAQK	RGPGAGNPAD	TLGQGHEDRP	

	51					100
FGF4	AELERRWESL	VALSLARLPV	AA..QPKEAA	VQSGAGDY..	...LLGIKRL	
FGF6	S...RGWGTL	LSRSRAGLAG	EI.....AG	VNWESG.Y..	...LVGIKRQ	
FGF5	SSSRQSSSSA	MSSSSASSSP	AASLGSQGS	LEQSSFQW..	...SPSGRRT	
FGF1MAEG	EITTF TALTE	KFN...LPPGN..	...YK...KP	
FGF2MAAG	SITTL PALPE	DGGSGAFPPGH..	...FK...DP	
FGF9	FGNVPVLPVD	SPVLLSDHLG	QSEAGGLPRG	PAVTDLDH..	...LKGILRR	
FGF7	LACNDMTPEQ	M...ATNVNCSSPE	RHTRSVDY..	...MEGGDIR	
KGF2	VTCQALGQDM	VSPEATNSSS	SSFSSPSSAG	RHVRSYNH..	...LQ.GDVR	
FGF3	PGWPAAGPGARLRRDAG	GRGGVYEH..	...L.GGAPR	
FGF8	FGQRSRAGKN	FTNPAPNYPE	EGSKEQRDSV	LPKVTQRHVR	EQSLVTDQLS	

MATCH WITH FIG. 2B

FIG. 2A

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MATCH WITH FIG. 2A

	101		150
FGF4	RRL.....YC	NVGIGFHLQA	LPDGRIGGAH ADT.RDSLLE LSPVERGV.V
FGF6	RRL.....YC	NVGIGFHLQV	LPDGRISGTH EEN.PYSLLE ISTVERGV.V
FGF5	GSL.....YC	RVGIGFHLQI	YPDGKVNGSH EAN.MLSVLE IFAVSQGI.V
FGF1	KLL.....YC	SNG.GHFLRI	LPDGTVDGTR DRSDQHIQLQ LSAESVGE.V
FGF2	KRL.....YC	KNG.GFFLRI	HPDGRVDGVR EKSDPHIKLQ LQAEERGV.V
FGF9	RQL.....YC	R.T.GFHLEI	FPNGTIQGTR KDHSRFGILE FISIAVGL.V
FGF7	VRR.....LF	CRT.QWYLRI	DKRGKVKGTQ EMKNNYNIME IRTVAVGI.V
KGF2	WRK.....LF	SFT.KYFLKI	EKNGKVSGTK KENCPSYLE ITSVEIGV.V
FGF3	RRK.....LY	CAT.KYHLQL	HPSGRVNGSL .ENSAYSILE ITAVEVGI.V
FGF8	RRLIRTYQLY	SRTSGKHVQV	LANKRINAMA EDGDPFAKLI VETDTFGSRV

	151		200
FGF4	SIFGVASRFF	VAMSSK GKLY	G.SPFFTDEC TFKEILLPNN YNAYESYKYP
FGF6	SLFGVRSALF	VAMNSKGRLY	A.TPSFQEEC KFRETLLPNN YNAYESDLYQ
FGF5	GIRGVFSNKF	LAMSKK GKLY	A.SAKFTDDC KFRERFQENS YNTYASAIHR
FGF1	YIKSTETGQY	LAMDTDGLLY	G.SQTPNEEC LFLERLEENH YNTYISKKH.
FGF2	SIKGVCANRY	LAMKEDGRLL	A.SKCVTDEC FFFERLESNN YNTYRSRKY.
FGF9	SIRGVDSGLY	LGMNEKGELY	G.SEKLTQEC VFREQFEENW YNTYSSNLYK
FGF7	AIKGVSESEFY	LAMNKEGKLY	A.KKECNEDC NFKELILENH YNTYAS....
KGF2	AVKAINSNNY	LAMNKK GKLY	G.SKEFNDC KLKERIEENG YNTYAS....
FGF3	AIRGLFSGRY	LAMNKRGRLY	A.SEHYSAEC EFVERIHELG YNTYASRLYR
FGF8	RVRGAETGLY	ICMNKK GKLY	AKSNGKGKDC VFTEIVLENN YTALQNAKY.

MATCH WITH FIG. 2C

FIG. 2B

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MATCH WITH FIG. 2B

	201		250
FGF4 GM..... FI	ALSKNGKTKK	G..NRVSPTM KVTHFLPRL.
FGF6 GT..... YI	ALSKYGRVVR	G..SKVSPIM TVTHFLPRI.
FGF5 TEKTGREWYV	ALNKRKAKR	GCSPRVKPOH ISTHFLPRFK
FGF1AEKNWFV	GLKKNGSCKR	G..PRTHYGQ KAILFLPLPV
FGF2T..SWYV	ALKRTGQYKL	G..SKTGPGQ KAILFLPMSA
FGF9	HV..... ..DTGRYYV	ALNKDGTPRE	G..TRTKRHQ KFTHFLPRPV
FGF7 AKW THNGGEM.FV	ALNQKGIPVR	G..KKTKEQ KTAHFLPMAI
KGF2 FNW QHNGRQM.YV	ALNGKGAPRR	G..QKTRRKN TSAHFLPMV
FGF3	TVSSTPGARR QPSAERLWYV	SVNGKGRPRR	G..FKTRRTQ KSSLFLPRVL
FGF8EGWYM	AFTRKGRPRK	G..SKTRQHQ REVHFMKRLP

	251		300
FGF4		
FGF6		
FGF5	QSEQPELSFT VTVPEKKNPP	SPIKSKIPLS	APRKNTNSVK YRLKFRFG..
FGF1	SSD.....		
FGF2	KS.....		
FGF9	DPDKVPELYK DILSQS....		
FGF7	T.....		
KGF2	HS.....		
FGF3	DHRDHEMVRQ LQSGLPRPPG	KGVPORRRRQ	KQSPDNLEPS HVQASRLGSQ
FGF8	RGHHTTEQSL RFEFLNYPPF	TRSLRGSQRT	WAPR.....

MATCH WITH FIG. 2D

FIG. 2C

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MATCH WITH FIG. 2C

	301
FGF4
FGF6
FGF5
FGF1
FGF2
FGF9
FGF7
KGF2
FGF3	LEASAH
FGF8

FIG.2D

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GGAATTCCGG GAAGAGAGGG AAGAAAACAA CGGCGACTGG GCAGCTGCCT CCACTTCTGA	60
CAACTCCAAA GGGATATACT TGTAAGAGTG GCTCGCAGGC TGGGGCTCCG CAGAGAGAGA	120
CCAGAAGGTG CCAACCGCAG AGGGGTGCAG ATATCTCCCC CTATTCCCCA CCCACCTCC	180
CTTGGGTTTT GTTCACCGTG CTGTCATCTG TTTTTCAGAC CTTTTTGGCA TCTAACATGG	240
TGAAGAAAGG AGTAAAGAAG AGAACAAAGT AACTCCTGGG GGAGCGAAGA GCGCTGGTGA	300
CCAACACCAC CAACGCCACC ACCAGCTCCT GCTGCTGCGG CCACCCACGT CCACCATTTA	360
CCGGGAGGCT CCAGAGGCGT AGGCAGCGGA TCCGAGAAAG GAGCGAGGGG AGTCAGCCGG	420
CTTTTCCGAG GAGTTATGGA TGTTGGTGCA TTCACTTCTG GCCAGATCCG CGCCAGAGG	480
GAGCTAACCA GCAGCCACCA CCTCGAGCTC TCTCCTTGCC TTGCATCGGG TCTTACCCTT	540
CCAGTATGTT CTTTCTGATG AGACAATTC CAGTGCCGAG AGTTTCAGTA CA ATG	595
Met	
TGG AAA TGG ATA CTG ACA CAT TGT GCC TCA GCC TTT CCC CAC CTG CCC	643
Trp Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu Pro	
GGC TGC TGC TGC TGC TGC TTT TTG TTG CTG TTC TTG GTG TCT TCC GTC	691
Gly Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser Val	
CCT GTC ACC TGC CAA GCC CTT GGT CAG GAC ATG GTG TCA CCA GAG GCC	739
Pro Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala	
ACC AAC TCT TCT TCC TCC TCC TTC TCC TCT CCT TCC AGC GCG GGA AGG	787
Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg	
CAT GTG CGG AGC TAC AAT CAC CTT CAA GGA GAT GTC CGC TGG AGA AAG	835
His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys	
CTA TTC TCT TTC ACC AAG TAC TTT CTC AAG ATT GAG AAG AAC GGG AAG	883
Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys	
GTC AGC GGG ACC AAG AAG GAG AAC TGC CCG TAC AGC ATC CTG GAG ATA	931
Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile	
ACA TCA GTA GAA ATC GGA GTT GTT GCC GTC AAA GCC ATT AAC AGC AAC	979
Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn	
TAT TAC TTA GCC ATG AAC AAG AAG GGG AAA CTC TAT GGC TCA AAA GAA	1027
Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu	
TTT AAC AAT GAC TGT AAG CTG AAG GAG AGG ATA GAG GAA AAT GGA TAC	1075
Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr	

FIG.3A

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AAT ACC TAT GCA TCA TTT AAC TGG CAG CAT AAT GGG AGG CAA ATG TAT Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr	1123
GTG GCA TTG AAT GGA AAA GGA GCT CCA AGG AGA GGA CAG AAA ACA CGA Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg	1171
AGG AAA AAC ACC TCT GCT CAC TTT CTT CCA ATG GTG GTA CAC TCA Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser	1216
TAGAGGAAGG CAACGTTTGT GGATGCAGTA AAACCAATGG CTCTTTTGCC AAGAATAGTG	1276
GATATTCTTC ATGAAGACAG TAGATTGAAA GGCAAAGACA CGTTGCAGAT GTCTGCTTGC	1336
TTAAAAGAAA GCCAGCCTTT GAAGGTTTTT GTATTCAGTG CTGACATATG ATGTTCTTTT	1396
AATTAGTTCT GTGTCATGTC TTATAATCAA GATATAGGCA GATCGAATGG GATAGAAGTT	1456
ATTCCCAAGT GAAAAACATT GTGGCTGGGT TTTTGTGTGT TGTGTCAAG TTTTGTTTT	1516
TAAACCTCTG AGATAGAACT TAAAGGACAT AGAACAATCT GTTGAAAGAA CGATCTTCGG	1576
GAAAGTTATT TATGGAATAC GAACTCATAT CAAAGACTTC ATTGCTCATT CAAGCCTAAT	1636
GAATCAATGA ACAGTAATAC GTGCAAGCAT TTAAGGAAA GCACTTGGGT CATATCATAT	1696
GCACAACCAA AGGAGTTCTG GATGTGGTCT CATGGAATAA TTGAATAGAA TTTAAAAATA	1756
TAAACATGTT AGTGTGAAAC TGTTCTAACA ATACAAATAG TATGGTATGC TTGTGCATTC	1816
TGCCTTCATC CCTTTCTATT TCTTTCTAAG TTATTTATTT AATAGGATGT TAAATATCTT	1876
TTGGGGTTTT AAAGAGTATC TCAGCAGCTG TCTTCTGATT TATCTTTTCT TTTTATTCAG	1936
CACACCACAT GCATGTTTAC GACAAAGTGT TTTTAAACT TGGCGAACAC TTCAAAAATA	1996
GGAGTTGGGA TTAGGGAAGC AGTATGAGTG CCCGTGTGCT ATCAGTTGAC TTAATTTGCA	2056
CTTCTGCAGT AATAACCATC AACAATAAAT ATGGCAATGC TGTGCCATGG CTTGAGTGAG	2116
AGATGTCTGC TATCATTTGA AAACATATAT TACTCTCGAG GCTTCCTGTC TCAAGAAATA	2176
GACCAGAAGG CCAAATTCTT CTCTTTCAAT ACATCAGTTT GCCTCCAAGA ATATACTAAA	2236
AAAAGGAAAA TTAATTGCTA AATACATTTA AATAGCCTAG CCTCATTATT TACTCATGAT	2296
TTCTTGCCAA ATGTCATGGC GGTAAAGAGG CTGTCCACAT CTCTAAAAAC CCTCTGTAAA	2356
TTCCACATAA TGCATCTTTC CCAAAGGAAC TATAAAGAAT TTGGTATGAA GCGCAACTCT	2416

FIG. 3B

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CCCAGGGGCT TAAACTGAGC AAATCAAATA TATACTGGTA TATGTGTAAC CATATACAAA	2476
AACCTGTTCT AGCTGTATGA TCTAGTCTTT ACAAACCAA ATAAACTTG TTTTCTGTAA	2536
ATTTAAAGAG CTTTACAAGG TTCCATAATG TAACCATATC AAAATTCATT TTGTTAGAGC	2596
ACGTATAGAA AAGAGTACAT AAGAGTTTAC CAATCATCAT CACATTGTAT TCCACTAAAT	2656
AAATACATAA GCCTTATTTG CAGTGTCTGT AGTGATTTTA AAAATGTAGA AAAATACTAT	2716
TTGTTCTAAA TACTTTTAAG CAATAACTAT AATAGTATAT TGATGCTGCA GTTTTATCTT	2776
CATATTTCTT GTTTTGAAAA AGCATTTTAT TGTTTGGACA CAGTATTTTG GTACAAAAAA	2836
AAAGACTCAC TAAATGTGTC TTAATAAGT TTAACCTTTG GAAATGCTGG CGTCTGTGA	2896
TTCTCCAACA AACTTATTTG TGTCAATACT TAACCAGCAC TTCCAGTTAA TCTGTTATTT	2956
TTAAAAATTG CTTTATTAAG AAATTTTTTG TATAATCCCA TAAAAGGTCA TATTTTCCC	3016
ATTCTTCAAA AAAACTGTAT TTCAGAAGAA ACACATTGA GGCAGTGTCT TTTGGCTTAT	3076
AGTTTAAATT GCATTTTCATC ATACTTTGCT TCCAAGTGC TTTTGGCAA ATGAGATTAT	3136
AAAAATGTTT AATTTTTGTG GTTGAATCT GGATGTTAAA ATTTAATTGG TAACTCAGTC	3196
TGTGAGCTAT AATGTAATGC ATTCCTATCC AACTAGGTA TCTTTTTTTC CTTTATGTTG	3256
AAATAATAAT GGCACCTGAC ACATAGACAT AGACCACCCA CAACCTAAAT TAAATGTTTG	3316
GTAAGACAAA TACACATTGG ATGACCACAG TAACAGCAAA CAGGGCACAA ACTGGATTCT	3376
TATTTACAT AGACATTTAG ATTACTAAAG AGGGCTATGT GTAAACAGTC ATCATTATAG	3436
TACTCAAGAC ACTAAACAG CTTCTAGCCA AATATATTAA AGCTTGACAG GGCCAAAAAT	3496
AGAAAACATC TCCCCTGTCT CTCCACATT TCCCTCACAG AAAGACAAA AACCTGCCTG	3556
GTGCAGTAGC TCACACCTGT AATCCCAGCA GTTTGGGAGA CTGTGGGAAG ATGGCTTGAG	3616
TCCAGGAGTT CTAGACAGGC CTGAGAAACC TAGTGAGACA TCCTTCTCTT AAACAAAACA	3676
AAACAAAACA AATGTAGCCA TGCCTGGTGG CATATACCTG TGGTCCCAAC TACTCAGGAG	3736
GCTGAAACGG AAGGATCTCT TGGGCCCCAG GAGTTTGAGG CTGCAGTGAG CTATAATCTT	3796
GCCATTGCAC TCCAGCCTGG GTGAAAAAGA GCCAGAAAGA AAGGAAAGAG AGAAAAGAGA	3856
AAAGAAAGAG AGAAAAGACA GAAAGACAGG AAGGAAGGAA GGAAGGAAGG AAGGAAGGAA	3916
GGAAGCAAGG AAAGAAGGAA GGAAGGAAAG AAGGGAGGGA AGGAAGGAGA GAGAAAGAAA	3976
GATTGTTTGG TAAGGAGTAA TGACATTCTC TTGCATTAA AAGTGGCATA TTTGCTTGAA	4036

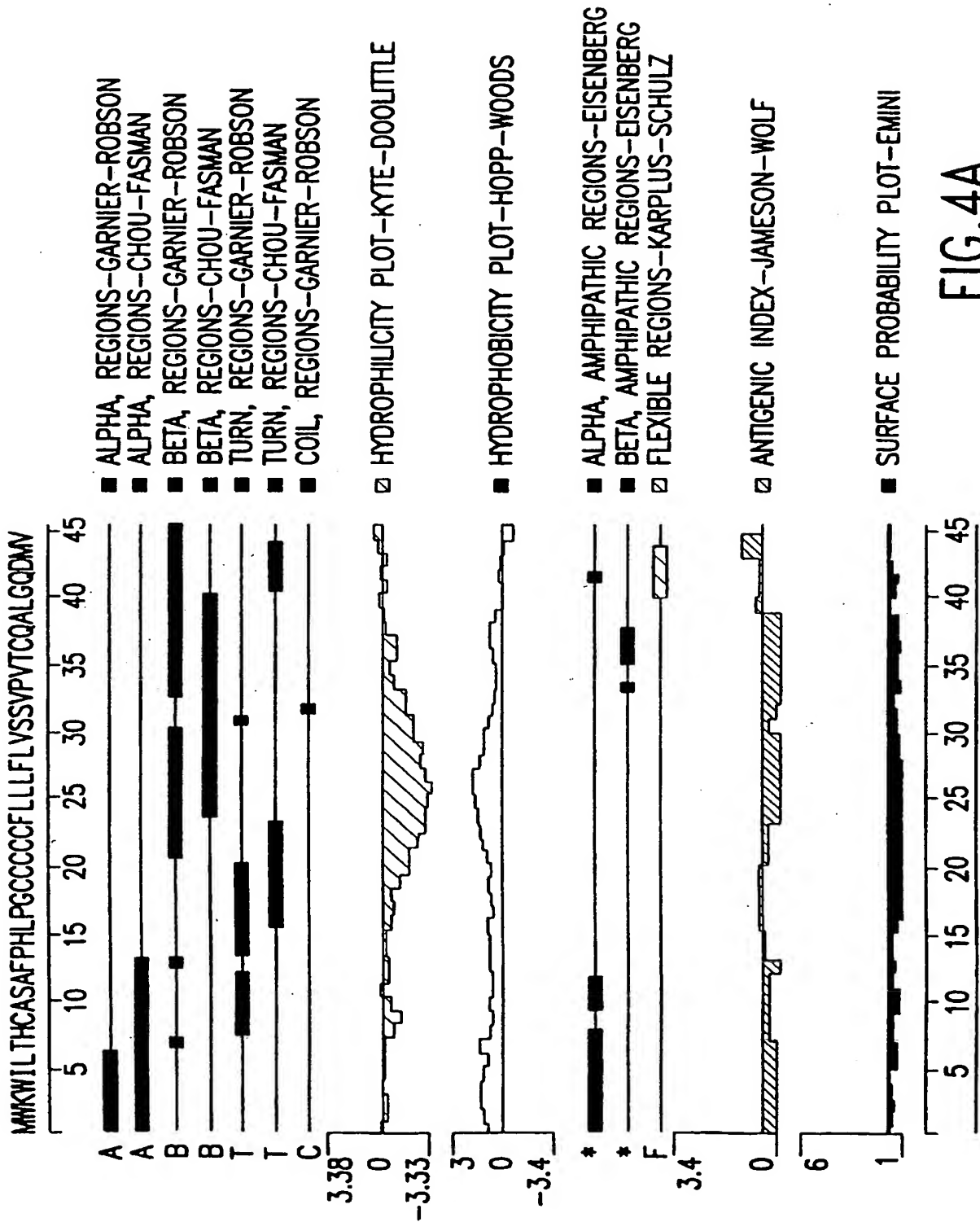
FIG.3C

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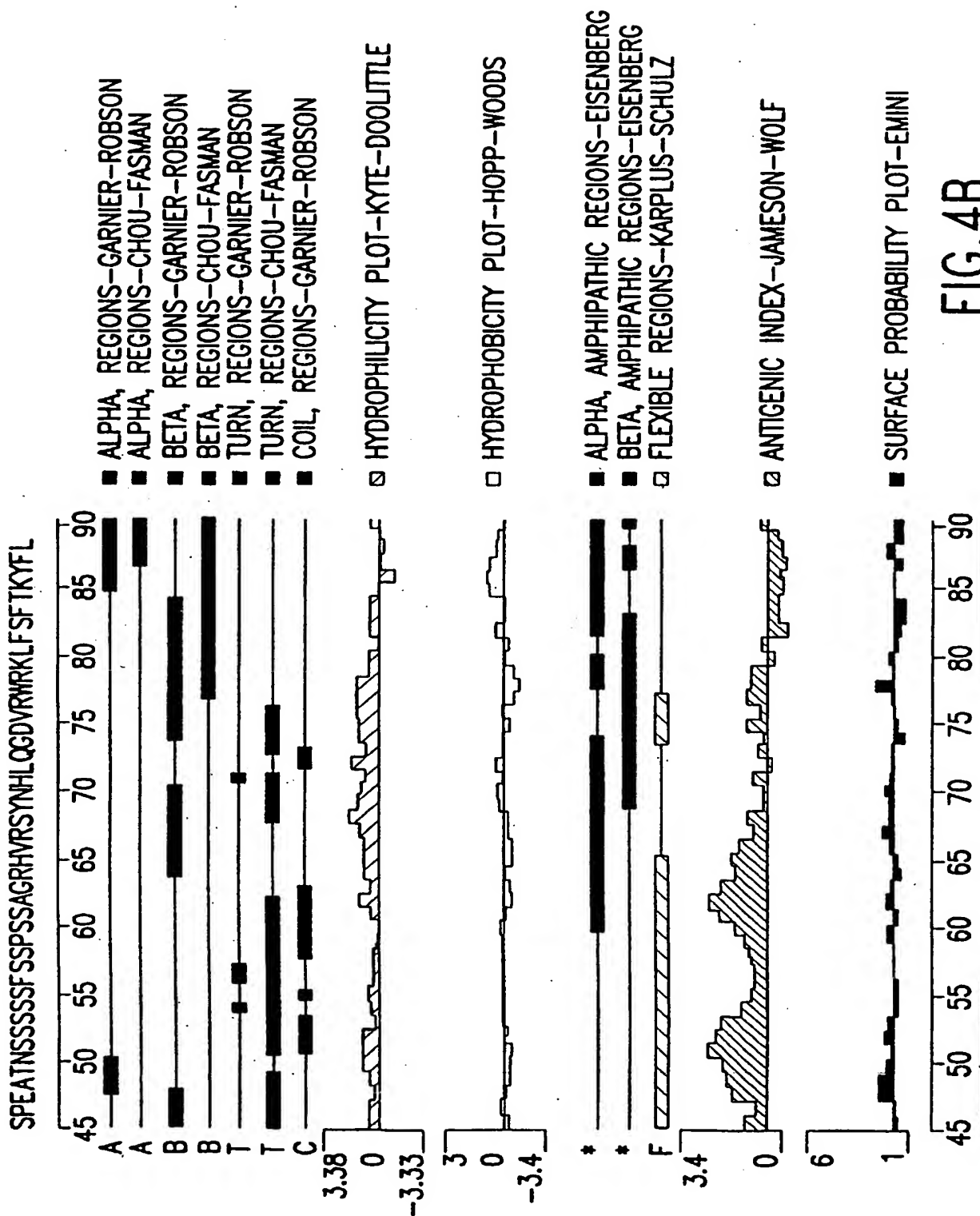
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TTCGCCCTAT AGTGAGTCGT A	4177

FIG.3D

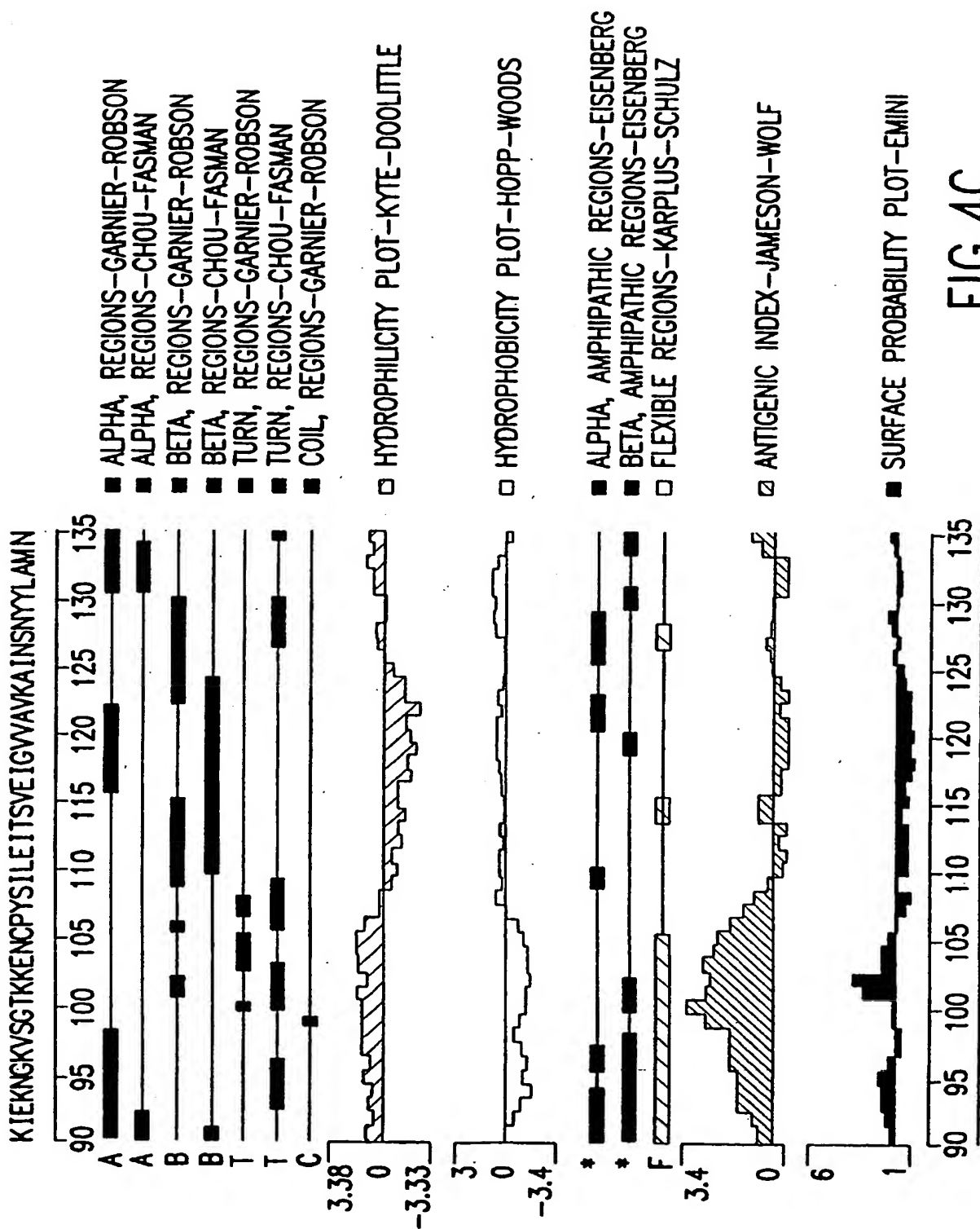
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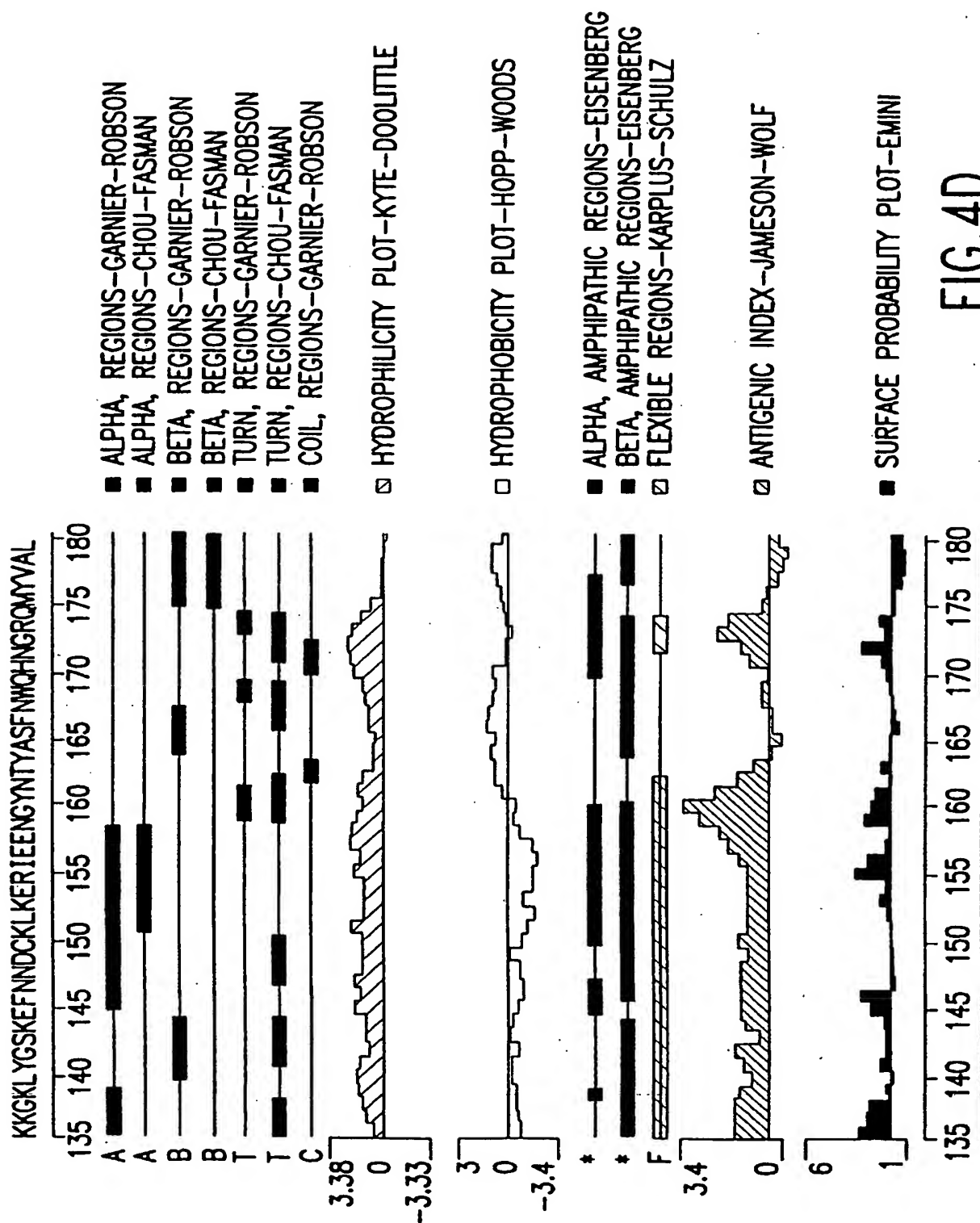
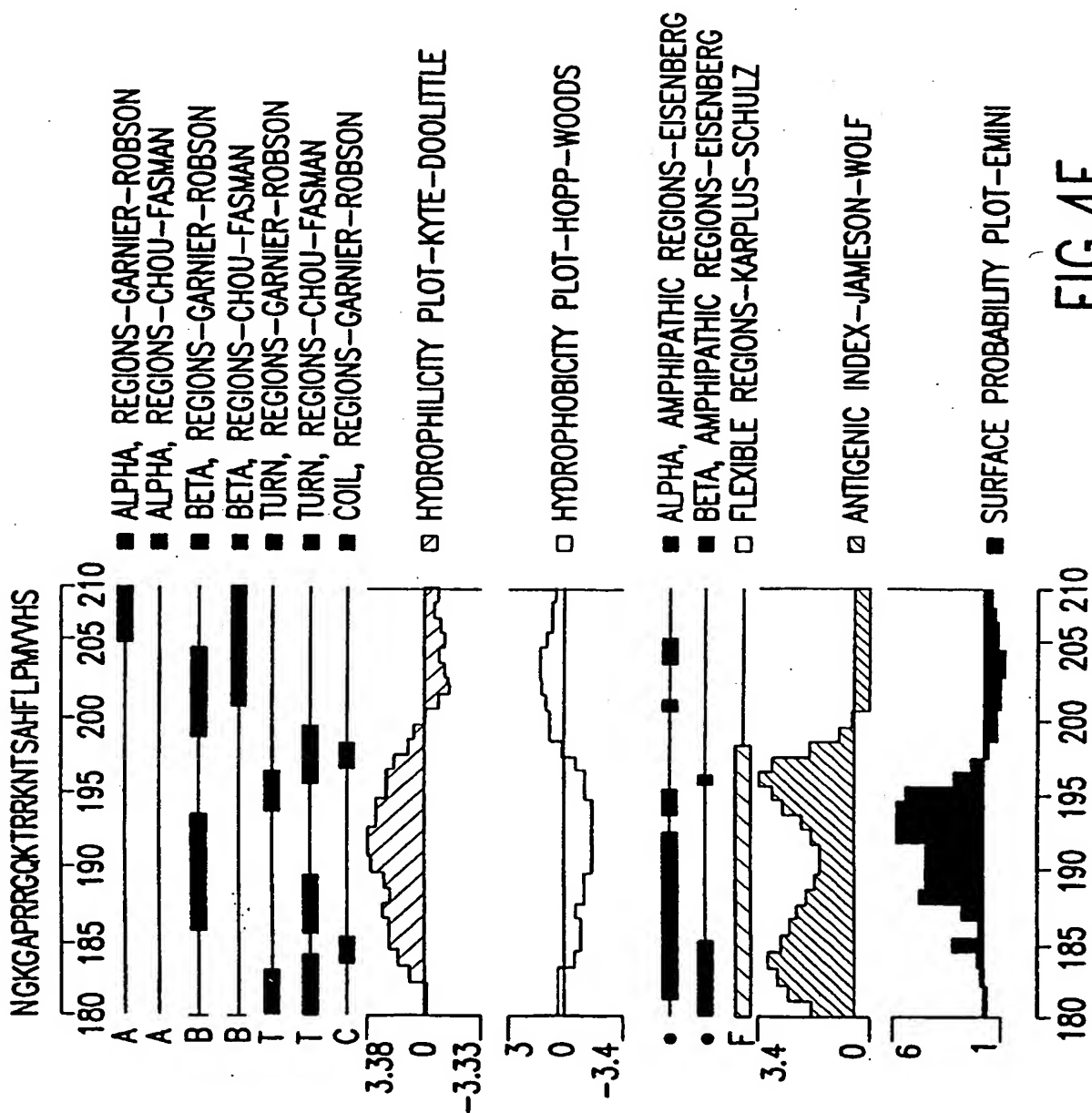


FIG.4D

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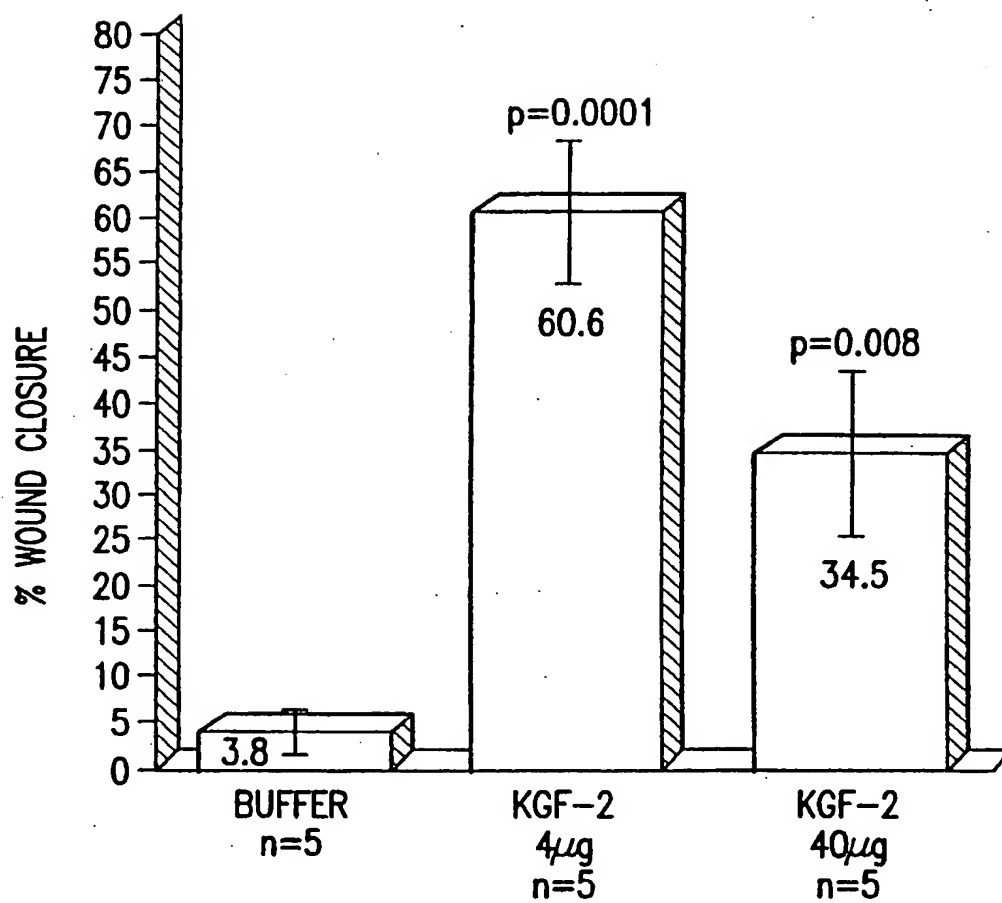


FIG.5

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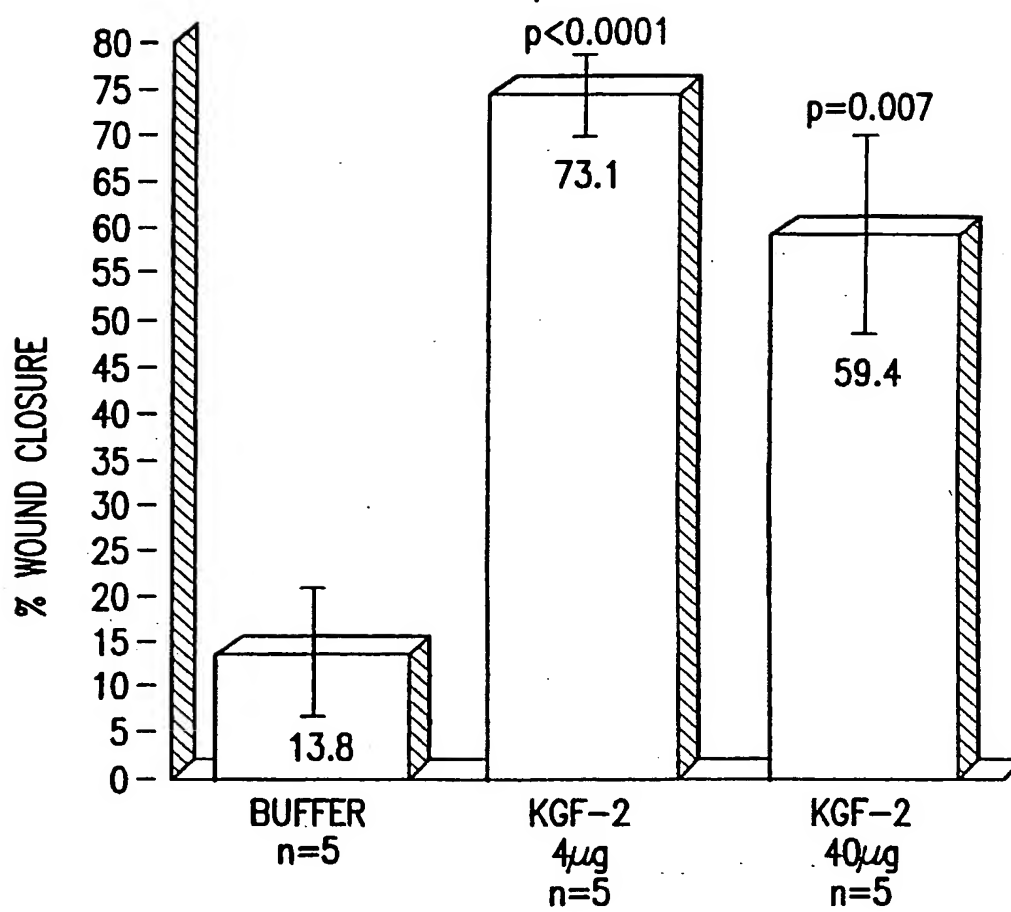


FIG.6

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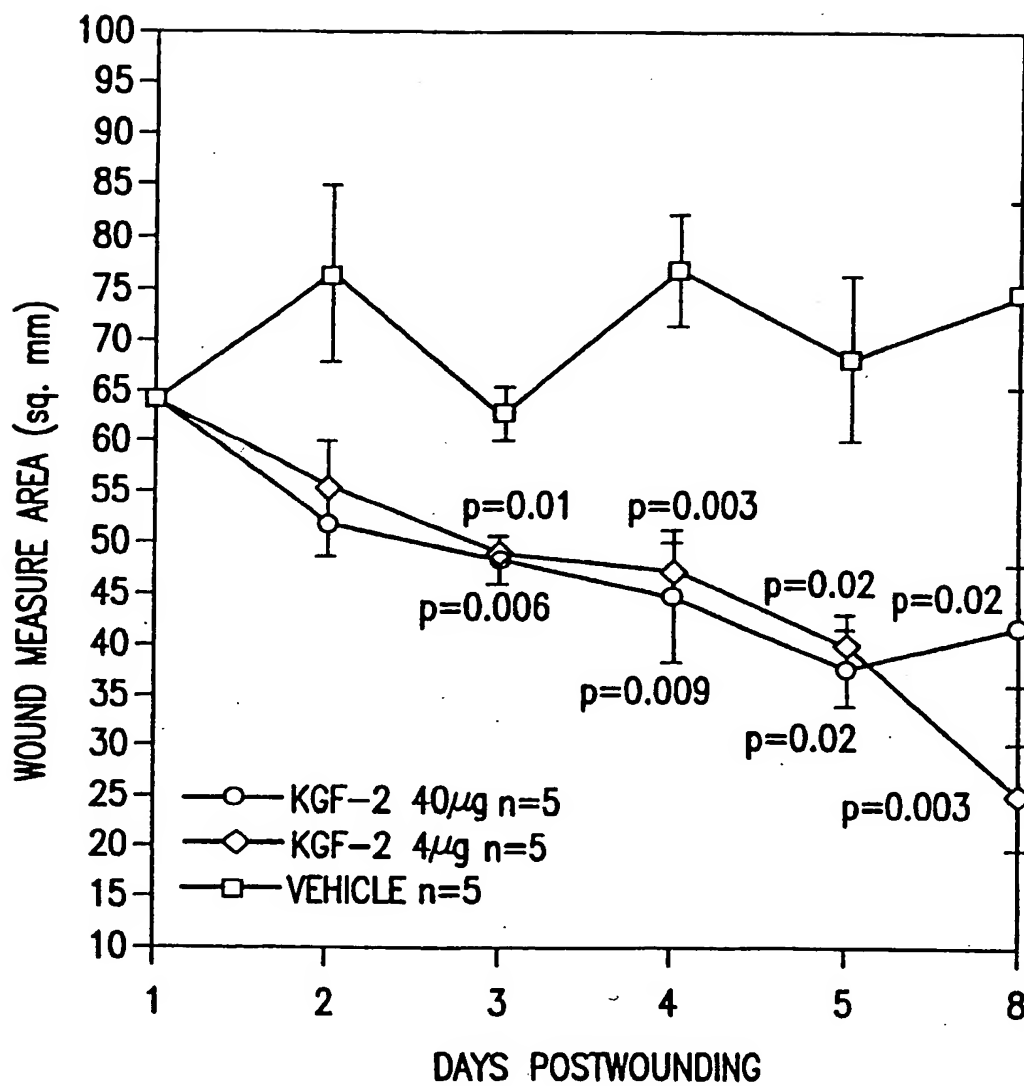


FIG.7

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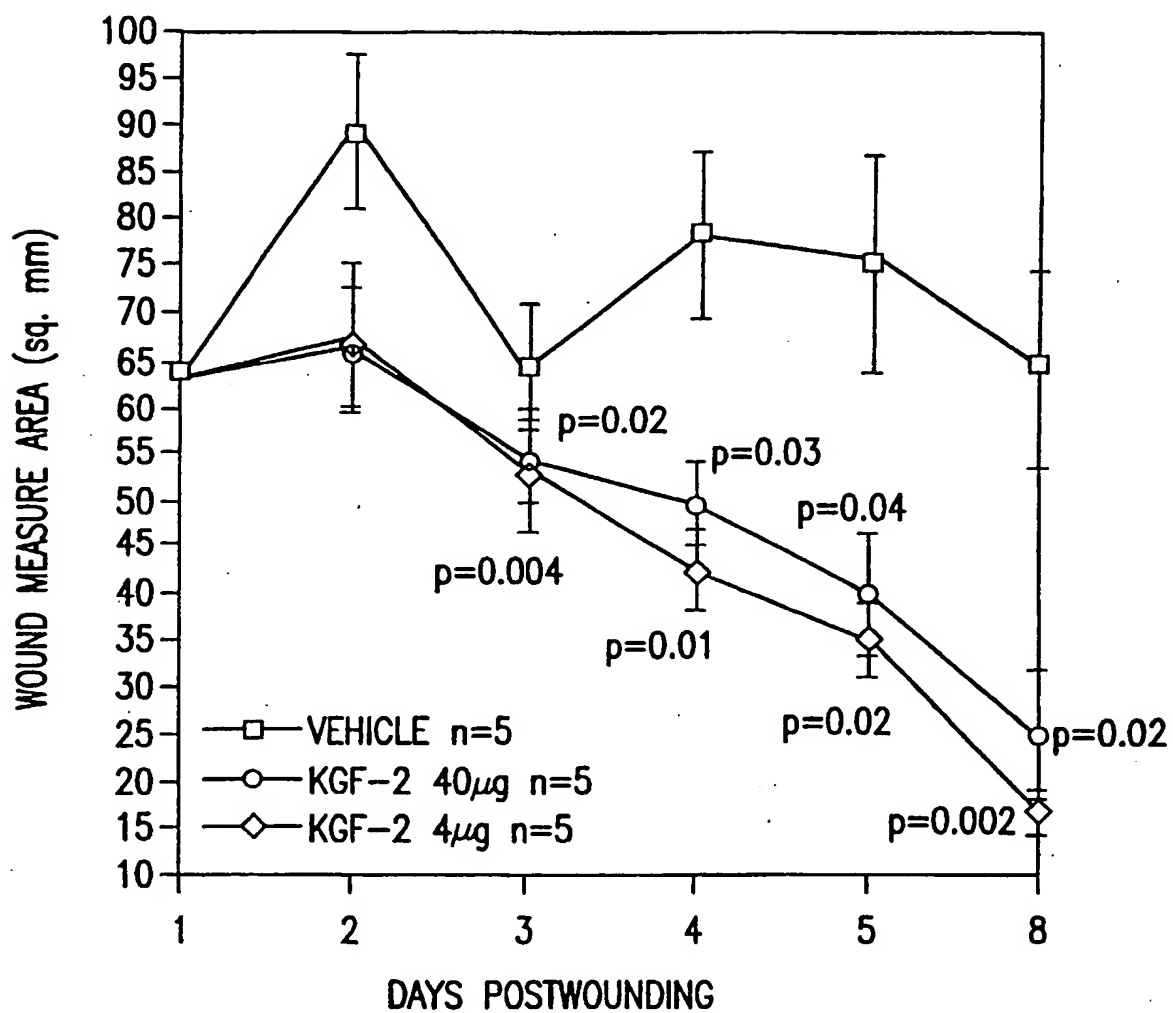
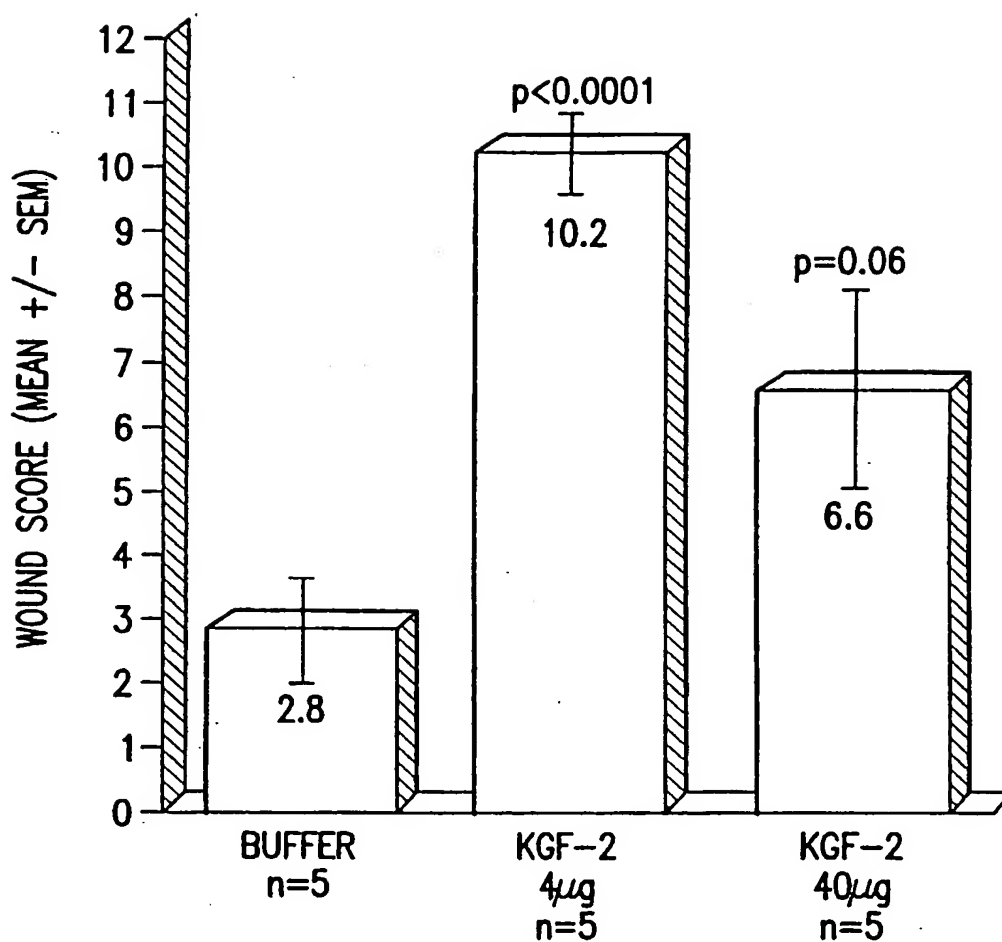


FIG.8

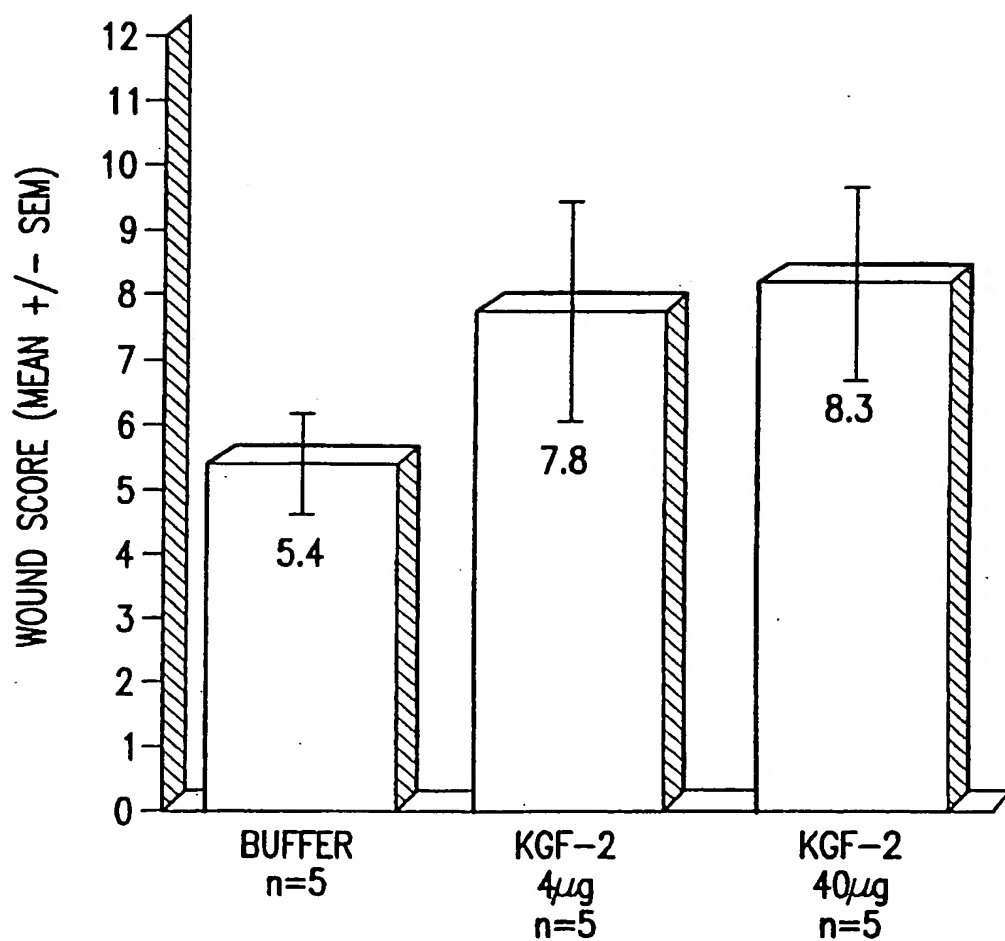
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1-3 MINIMAL CELL ACCUMULATION, NO GRANULATION
4-6 IMMATURE GRANULATION, INFLAMMATORY CELLS, CAPILLARIES
10-12 FIBROBLASTS, COLLAGEN, EPITHELIUM

FIG.9

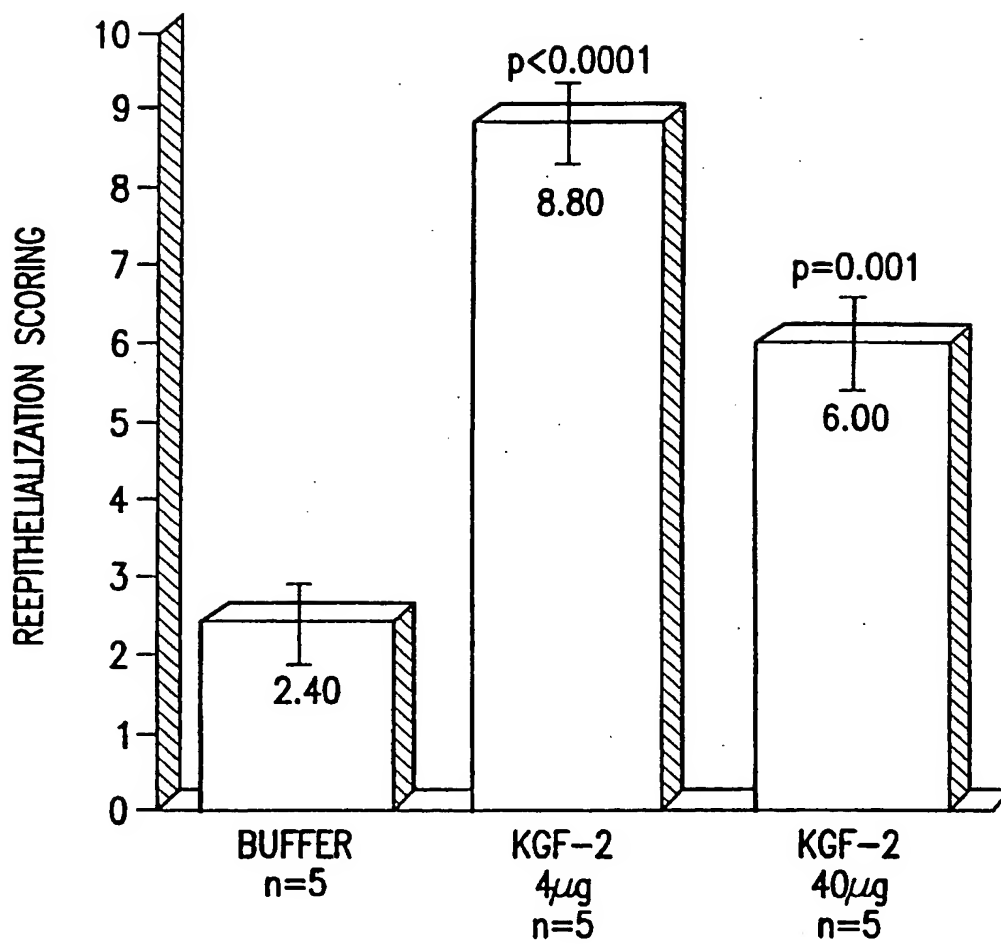
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1-3 MINIMAL CELL ACCUMULATION, NO GRANULATION
4-6 IMMATURE GRANULATION, INFLAMMATORY CELLS, CAPILLARIES
7-9 GRANULATION TISSUE, CELLS, FIBROBLASTS, NEW EPITHELIUM
10-12 FIBROBLASTS, COLLAGEN, EPITHELIUM

FIG.10

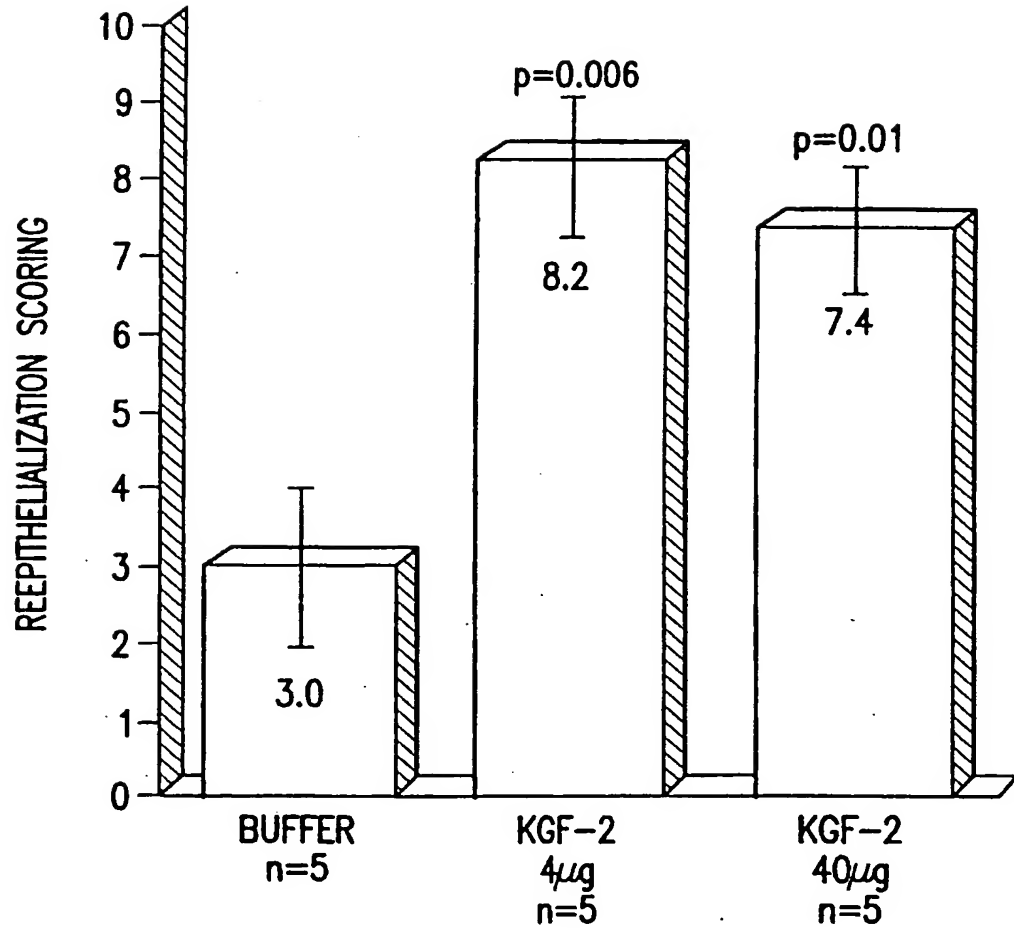
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ANTI-CYTOKERATIN IMMUNOSTAINING
0-NO CLOSURE
5-SLIGHT TO MODERATE CLOSURE
10-COMPLETE CLOSURE

FIG.11

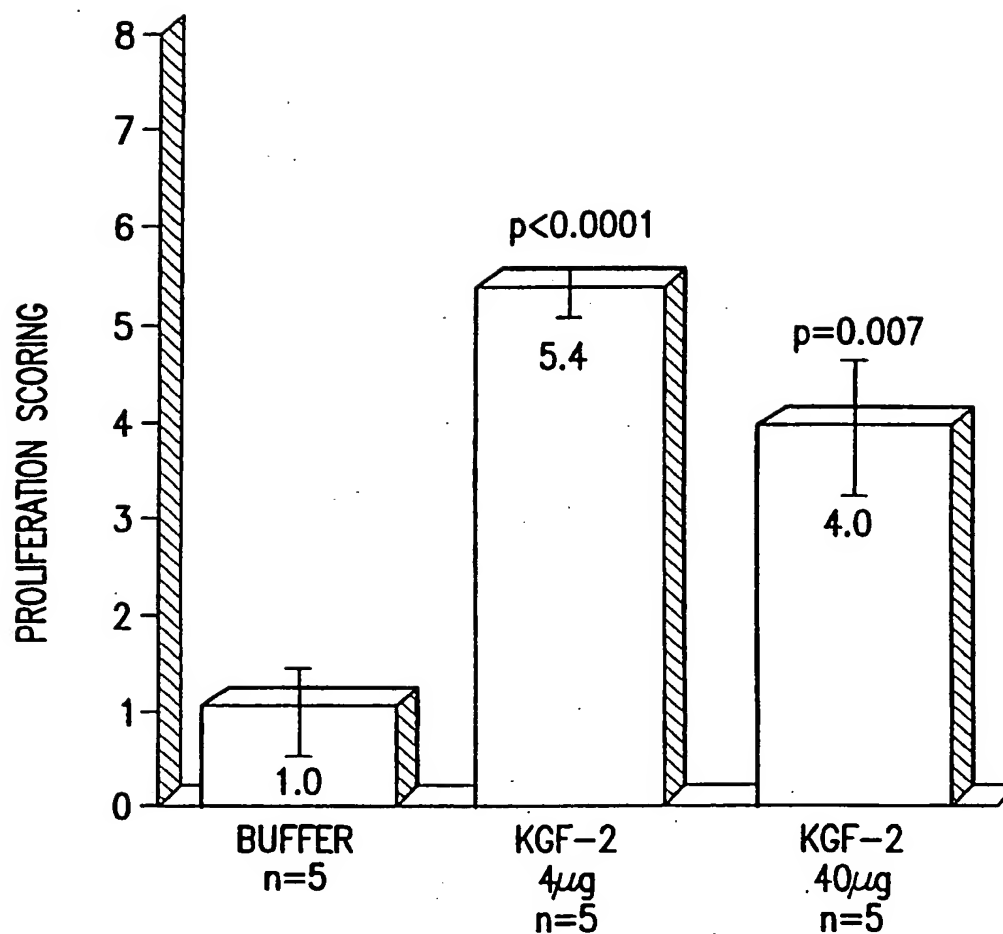
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ANTI-CYTOKERATIN IMMUNOSTAINING
0-NO CLOSURE
5-SLIGHT TO MODERATE CLOSURE
10-COMPLETE CLOSURE

FIG.12

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PCNA SCORING
0-2 SLIGHT PROLIFERATION
3-5 MODERATE PROLIFERATION
6-8 INTENSE PROLIFERATION

FIG.13

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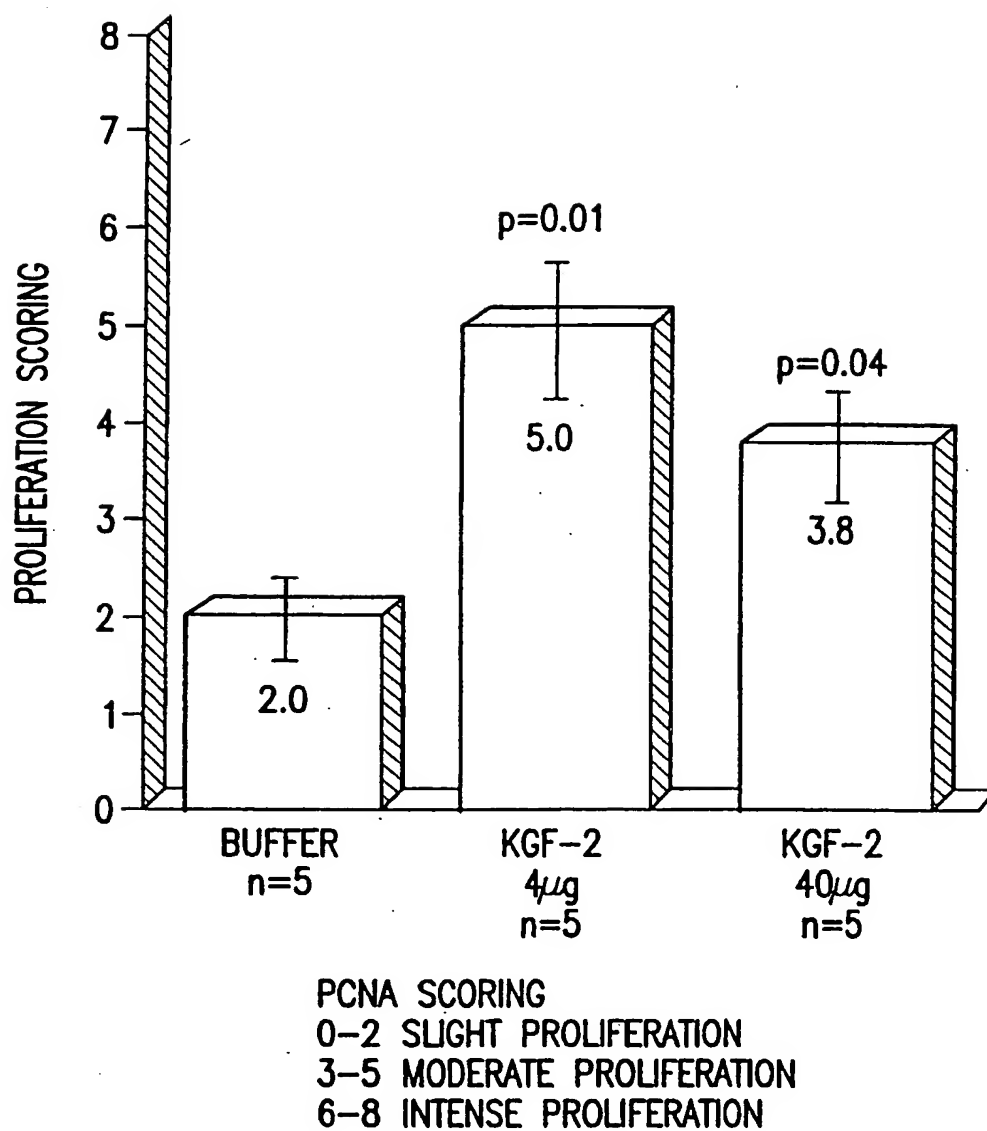


FIG.14

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ATGAGAGGATCGCATCACCATCACCATCACGGATCCTGCCAGGCTCTGGGTC
AGGACATGGTTTCTCCGGAAGCTACCAACTCTTCCTCTTCCTCTTTCTCTTCCC
CGTCTTCCGCTGGTCGTACGTTGTTCTTACAACCACCTGCAGGGTGACGTTT
GTTGGCGTAAACTGTTCTCTTTCACCAAATACTTCCTGAAAATCGAAAAA
AACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCATCCTG
GAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAAACAG
CAACTATTACTTAGCCATGAACAAGAAGGGGAACTCTATGGCTCAAAAG
AATTTAACAATGACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGAT
ACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGGCAAATGTAT
GTGGCATTGA_aTGGAAAAGGAGCTCCA_aGGAGAGGACAGAAAACACGAAG
GAAAAACACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAG

MRGSHHHHHHGSCQALGQDMVSPEATNSSSSSFSSPSSAGRHVRSYNHLQGD
VRWRKLFSTKYFLKIEKNGKVSGTKKENCPYSILEITSVEIGVVAVKAINSN
YYLAMNKKGKLYGSKEFNNDCKLKERIEENGYNTYASFNQHNQRQMYVA
LNGKGAPRRGQKTRRKNTSAHFLPMVHS

kgf-2 synthetic cys37 Bam HI
AAAGGATCCTGCCAGGCTCTGGGTCAGGACATG

FIG.15

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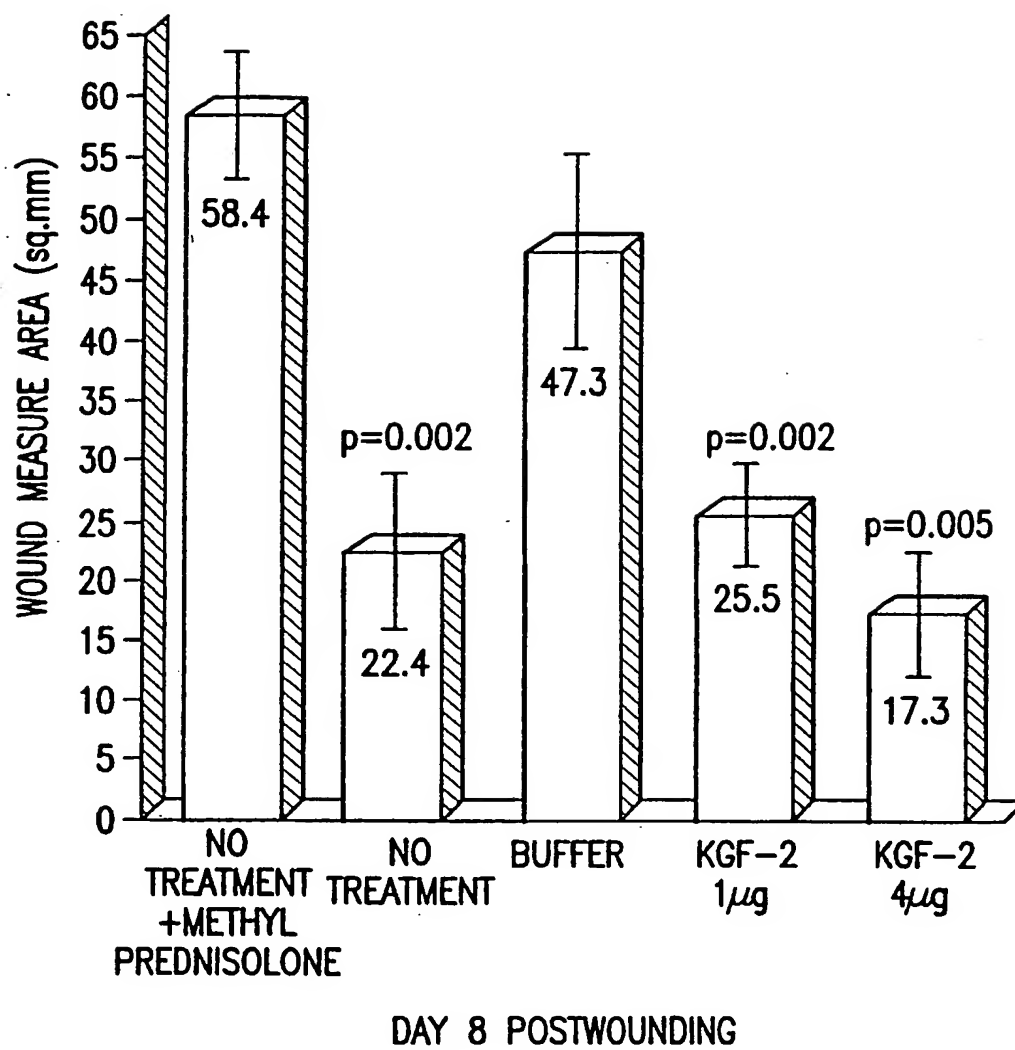
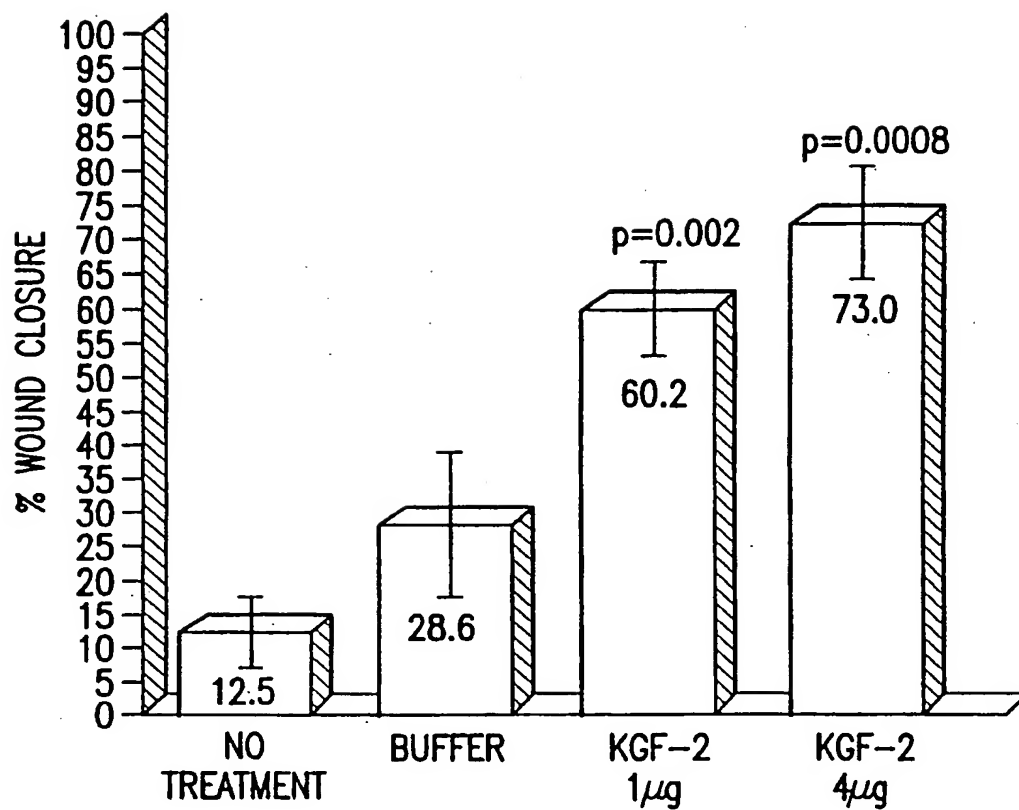


FIG.16

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GLUCOCORTICOID TREATED ANIMALS

FIG.17

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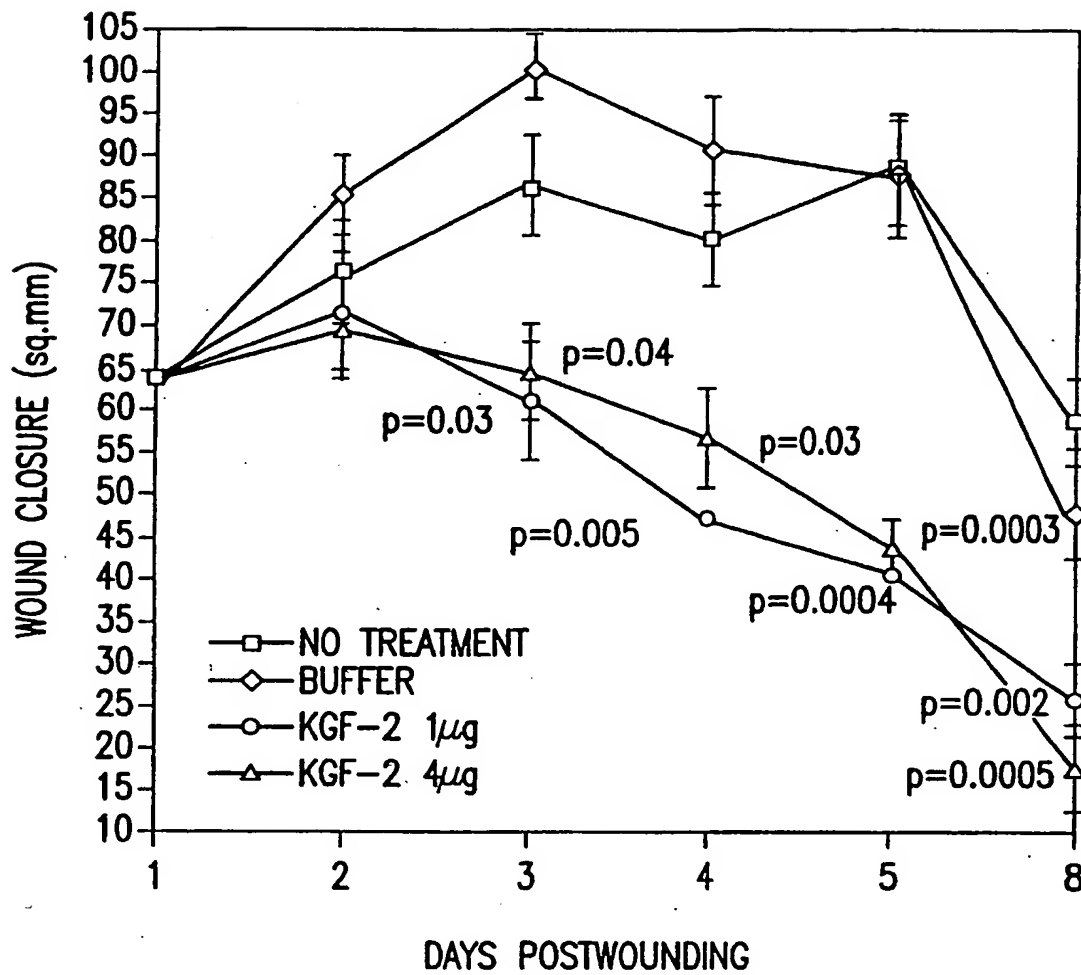


FIG.18

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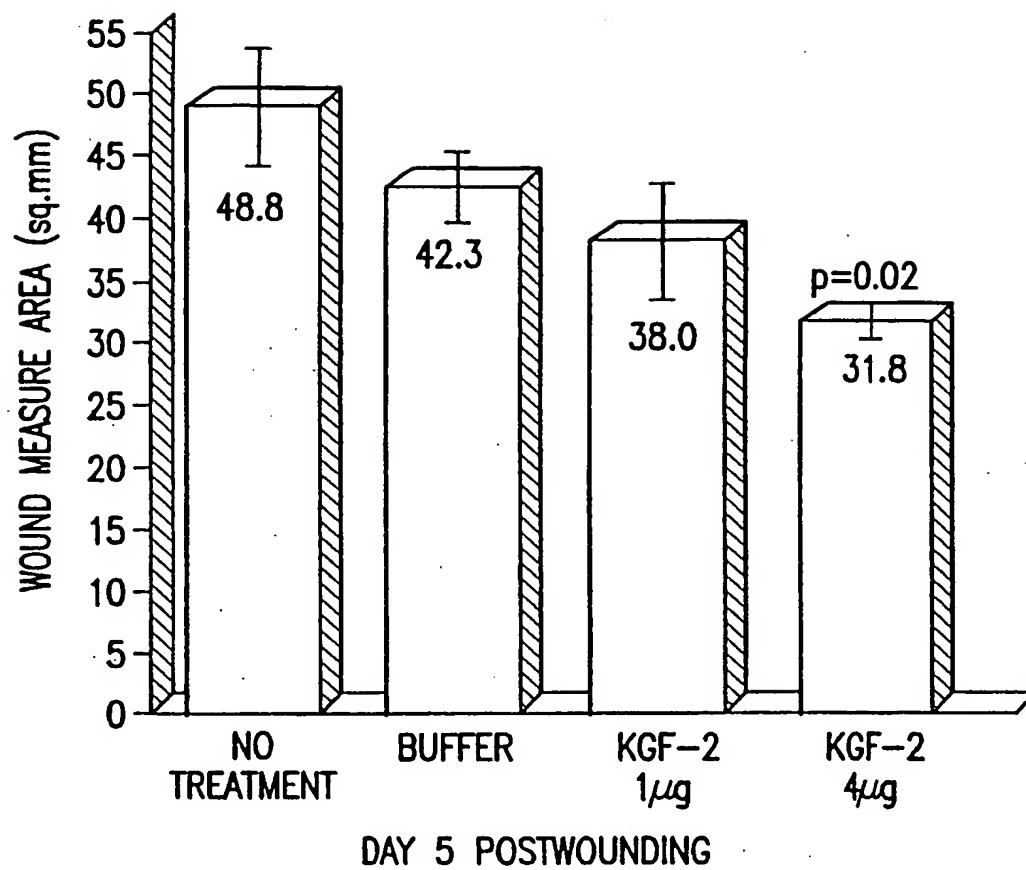


FIG.19A

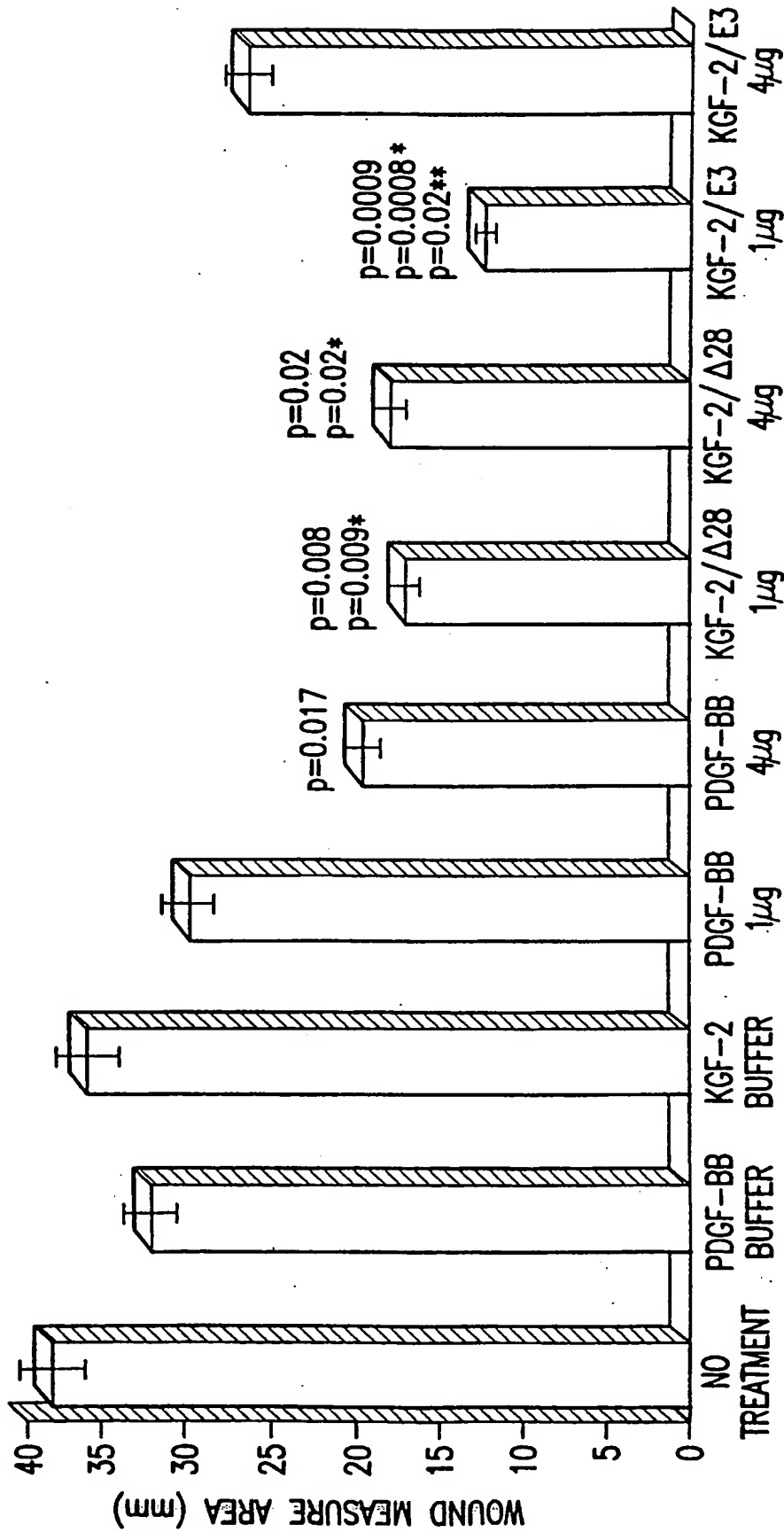


FIG.19B

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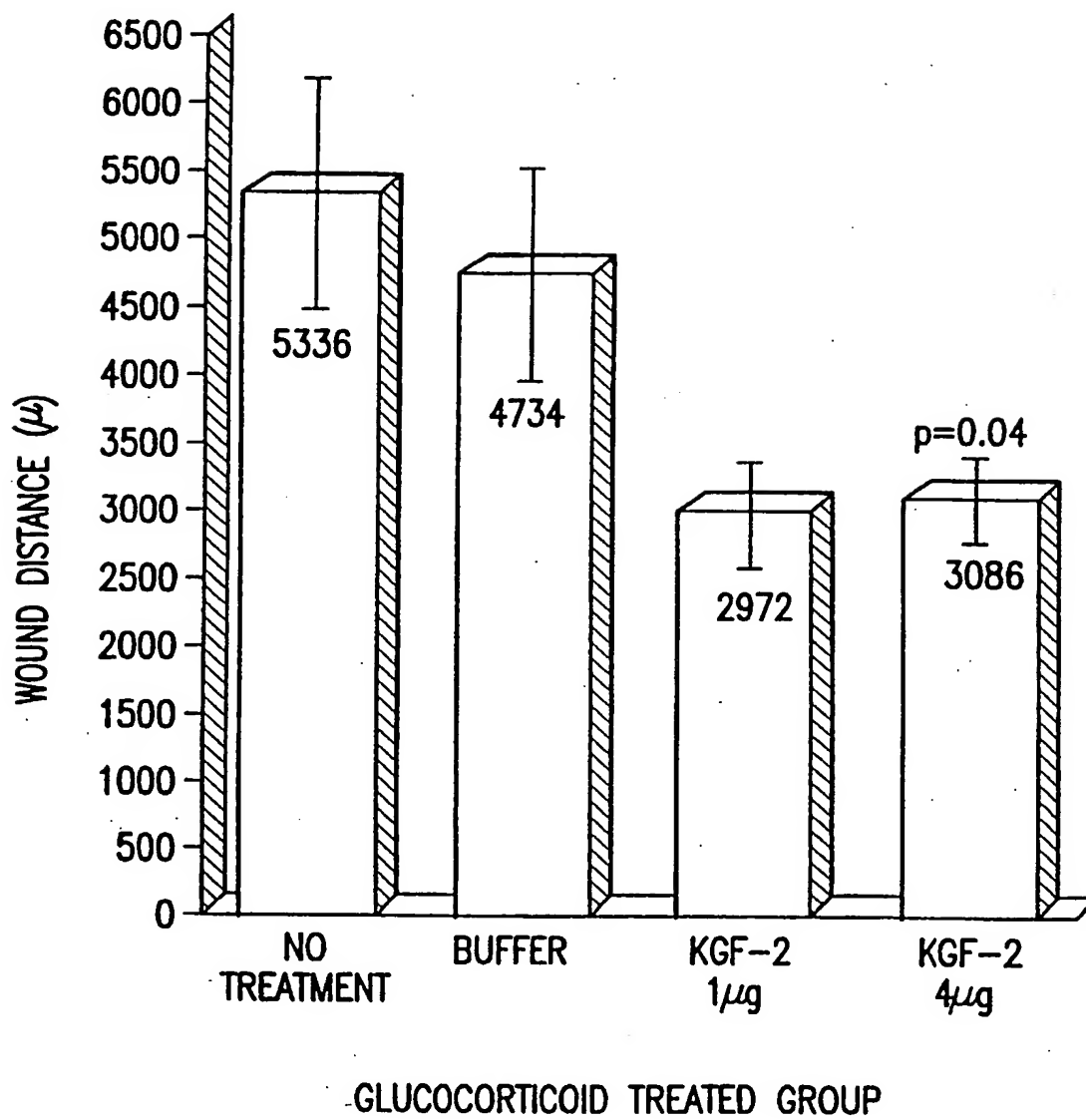


FIG.20

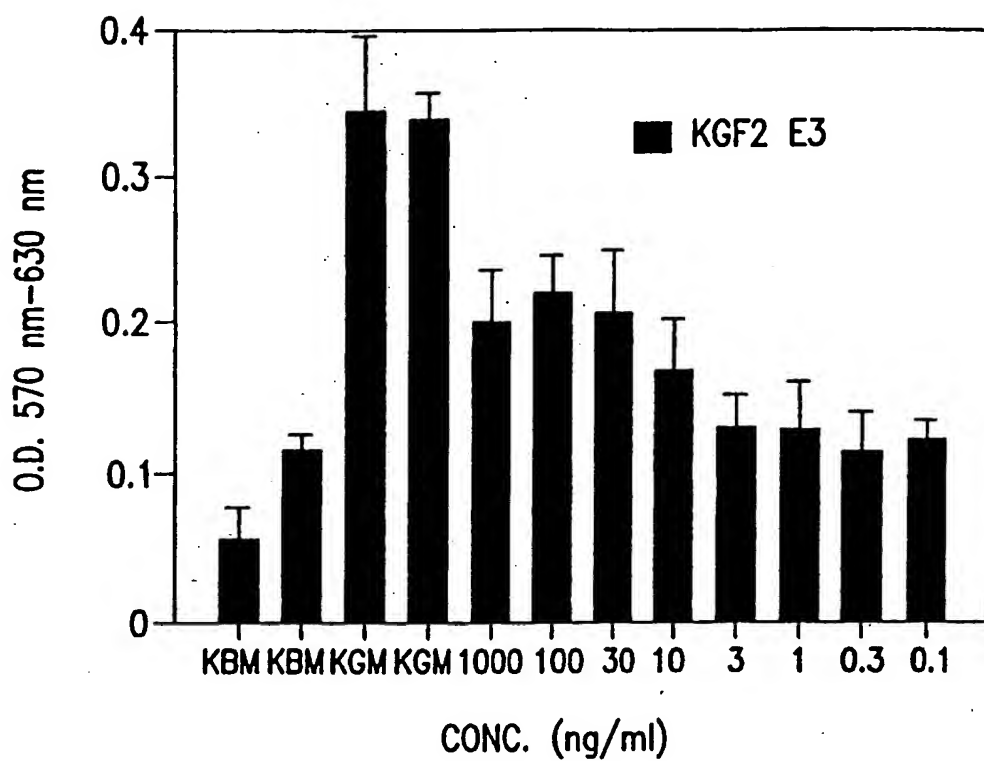


FIG.21A

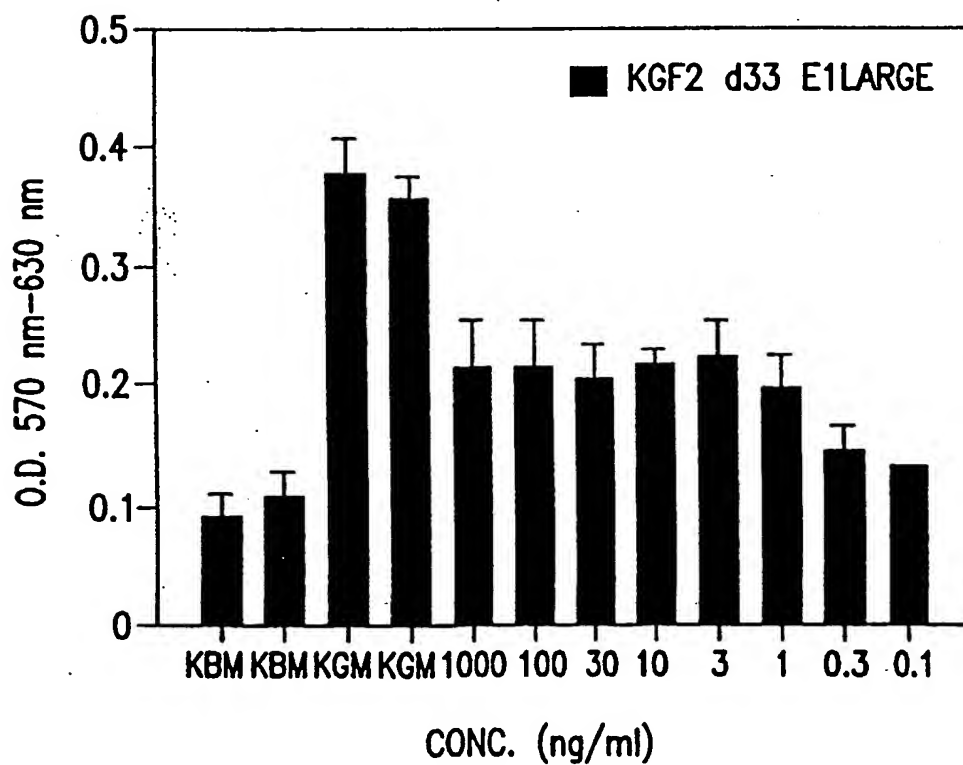


FIG.21B

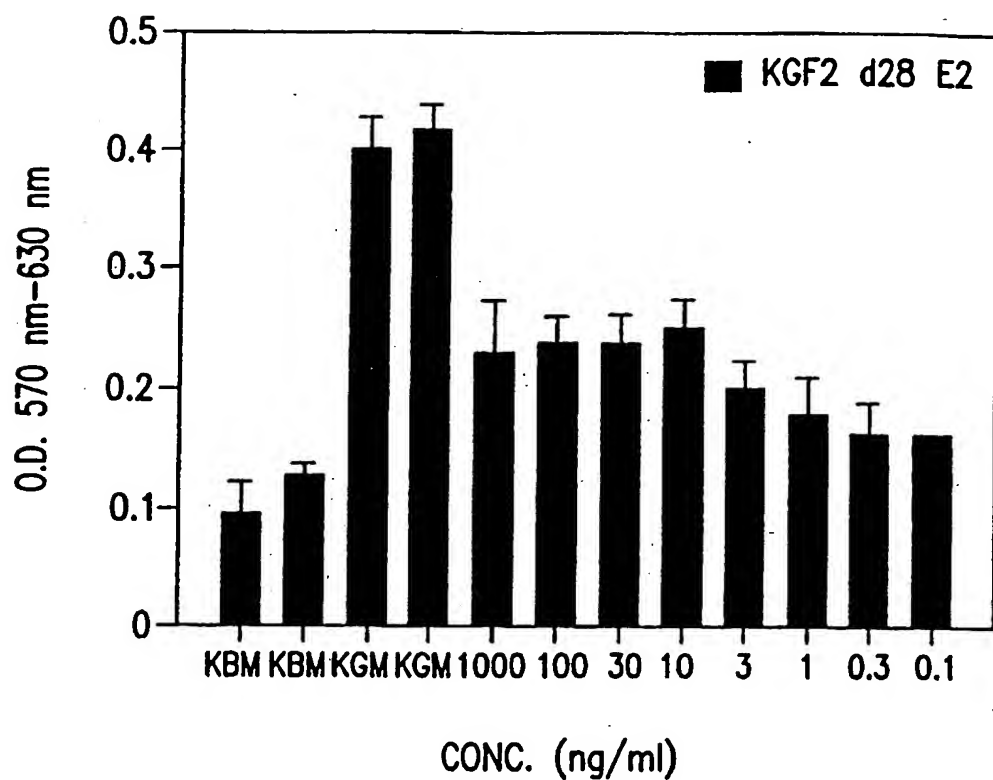


FIG.21C

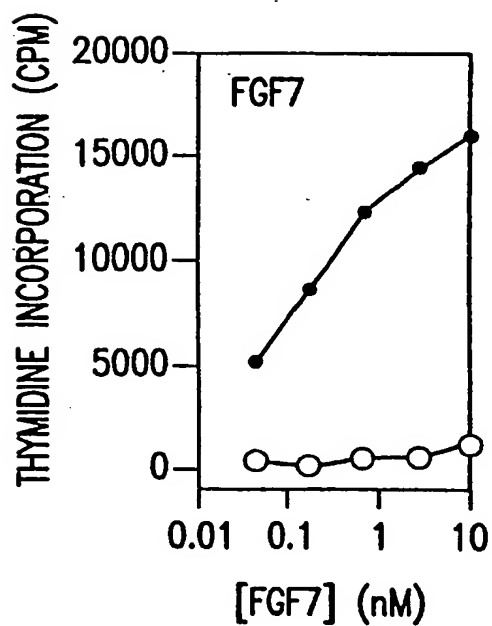


FIG.22A

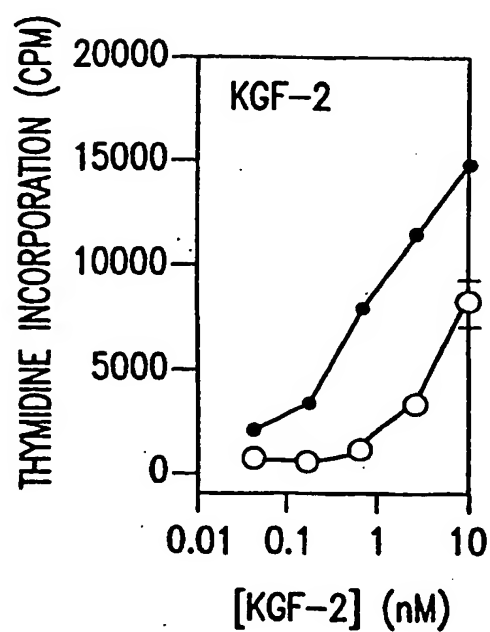


FIG.22A-1

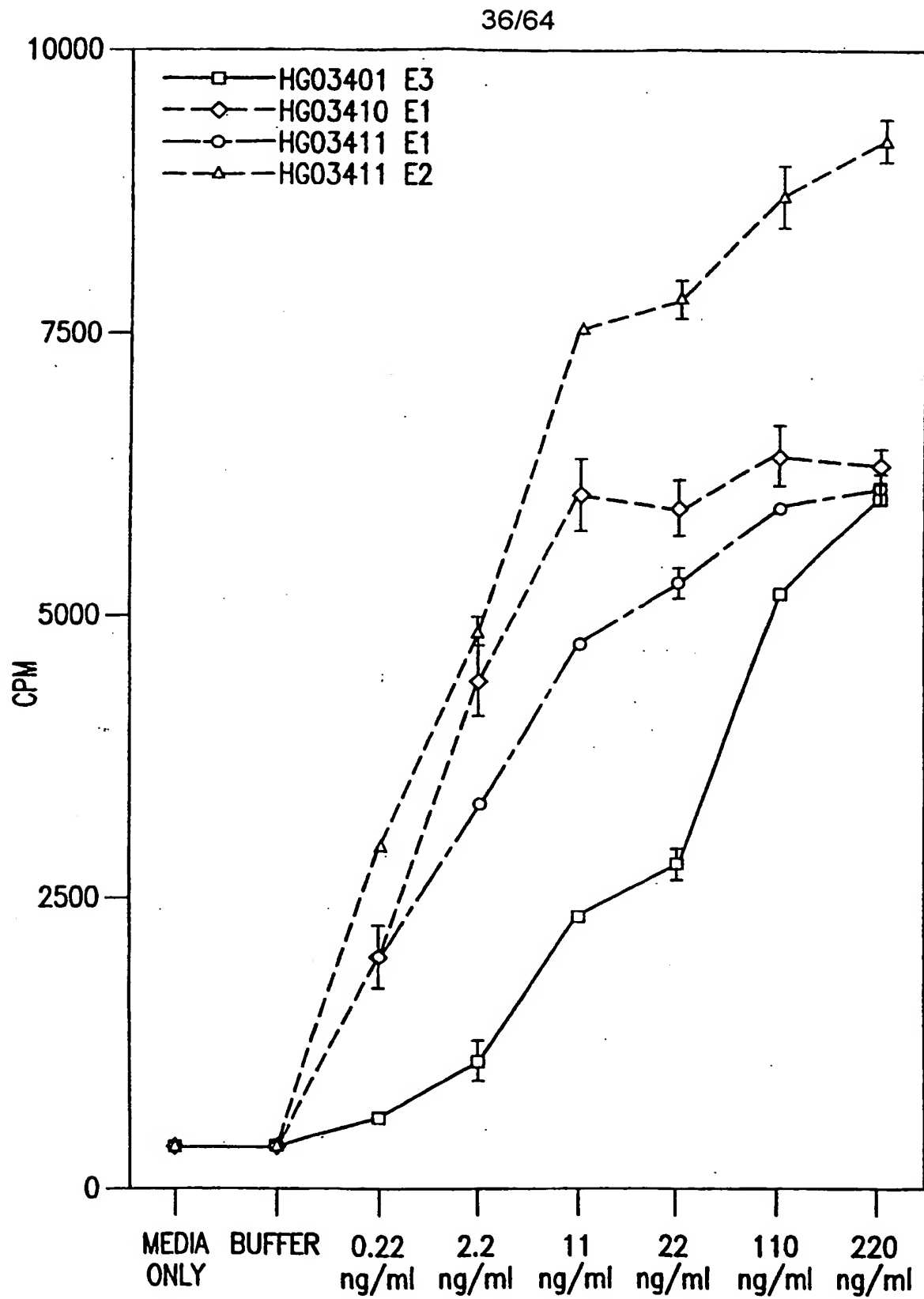


FIG.22B

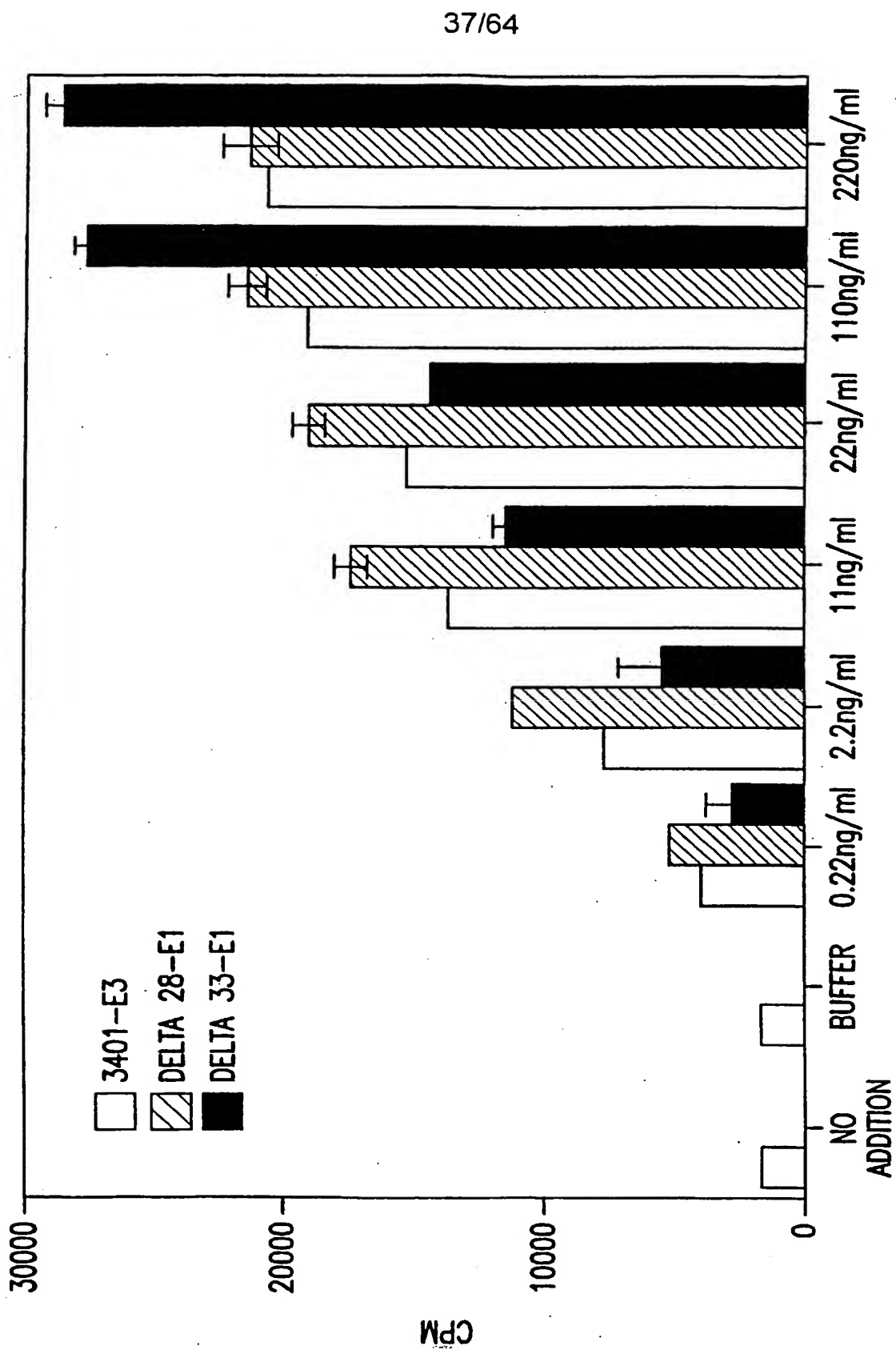


FIG.22C

ATGTGGAATGGATACTGACCCACTGCGCTTCTGCTTTCCCGCACCTGCCGGGTTGCTGC 60
Met Trp Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu Pro Gly Cys Cys

TGCTGCTGCTTCCTGCTGCTGTTCTTGTTTCTTCTGTTCCGGTTACCTGCCAGGCTCTG 120
Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser Val Pro Val Thr Cys Gln Ala Leu

GGTCAGGACATGGTTTCTCCGGAAGCTACCAACTCTTCCTCTTCCTCTTTCTCTTCCCCG 180
Gly Gln Asp Met Val Ser Pro Glu Ala Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro

ACTTCCGCTGGTCGTCACGTTCTTACAACCACCTGCAGGGTGACGTTTCGTTGGCGT 240
Thr Ser Ala Gly Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg

AAACTGTTCTCTTTCACCAAATACTTCCTGAAAATCGAAAAAACGGTAAAGTTTCTGGG 300
Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser Gly

ACCAAGAAGGAGAACTGCCCCGTACAGCATCCTGGAGATAACATCAGTAGAAATCGGAGTT 360
Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val

GTTGCCGTCAAAGCCATTAAACAGCAACTATTACTTAGCCATGAACAAGAAGGGGAAACTC 420
Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu

TATGGCTCAAAGAATTTAACAATGACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGA 480
Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly

TACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTG 540
Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu

AATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGGAAAAACACCTCTGCTCAC 600
Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His

TTTCTTCCAATGGTGGTACACTCATAG 627
Phe Leu Pro Met Val Val His Ser *

FIG. 23

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ATGACCTGCCAGGCTCTGGGTCAGGACATGGTTTCTCCGGAAGCTACCAACTCTTCCTCT 60
MetThrCysGlnAlaLeuGlyGlnAspMetValSerProGluAlaThrAsnSerSerSer

TCCTCTTTCTCTTCCCCGTCTTCCGCTGGTCGTCACGTTCTTACAACCACCTGCAG 120
SerSerPheSerSerProSerSerAlaGlyArgHisValArgSerTyrAsnHisLeuGln

GGTGACGTTGTTGGCGTAACTGTTCTCTTTCACCAAATACTTCCTGAAAATCGAAAAA 180
GlyAspValArgTrpArgLysLeuPheSerPheThrLysTyrPheLeuLysIleGluLys

AACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCCGTACAGCATCCTGGAGATAACA 240
AsnGlyLysValSerGlyThrLysLysGluAsnCysProTyrSerIleLeuGluIleThr

TCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAAACAGCAACTATTACTTAGCCATG 300
SerValGluIleGlyValValAlaValLysAlaIleAsnSerAsnTyrTyrLeuAlaMet

AACAAGAAGGGGAACTCTATGGCTCAAAAGAATTTAACAATGACTGTAAGCTGAAGGAG 360
AsnLysLysGlyLysLeuTyrGlySerLysGluPheAsnAsnAspCysLysLeuLysGlu

AGGATAGAGGAAAATGGATACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGG 420
ArgIleGluGluAsnGlyTyrAsnThrTyrAlaSerPheAsnTrpGlnHisAsnGlyArg

CAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGG 480
GlnMetTyrValAlaLeuAsnGlyLysGlyAlaProArgArgGlyGlnLysThrArgArg

AAAAACACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAG 525
LysAsnThrSerAlaHisPheLeuProMetValValHisSer *

FIG.24A

ATGACTTGCCAGGCACTGGGTCAAGACATGGTTTCCCCGAAGCTACCAACAGCTCCAGCTCTAGCTTCA
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----| 70
TACTGAACGGTCCGTGACCCAGTTCTGTACCAAAGGGCCCTTCGATGGTTGTCGAGGTCGAGATCGAAGT
M T C Q A L G Q D M V S P E A T N S S S S S F
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
GCAGCCCATCTAGCGCAGGTGTCACGTTGCTCTTACAACCACTTACAGGGTGATGTTGCTTGGCGCAA
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----| 140
CGTCGGGTAGATCGGTCCAGCAGTGCAAGCGAGAATGTTGGTGAATGTCCCACTACAAGCAACCGCGTT
S S P S S A G R H V R S Y N H L Q G D V R W R K
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
ACTGTTCACTTTACCAAGTACTTCTGAAAATCGAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAG
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----| 210
TGACAAGTCGAAATGGTTCATGAAGGACTTTTAGCTTTTTTGGCATTTCAAAGACCCTGGTTCTTCCTC
L F S F T K Y F L K I E K N G K V S G T K K E
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
AACTGCCCCGTACAGCATCCTCGAGATAACATCAGTAGAAATCGGAGTTGTTGCGTCAAAGCCATTAACA
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----| 280
TTGACGGGCATGTGCTAGGACCTCTATTGTAGTCATCTTAGCCTCAACAACGGCAGTTTCGGTAATTGT
N C P Y S I L E I T S V E I G V V A V K A I N
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
GCAACTATTACTTAGCCATGAACAAGAAGGGGAACTCTATGGCTCAAAGAATTTAACAATGACTGTAA
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----| 350
CGTTGATAATGAATCGGTACTTGTCTTCCCTTTGAGATACCGAGTTTCTTAAATTGTTACTGACATT
S N Y Y L A M N K K G K L Y G S K E F N N D C K
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
GCTGAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGG
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----| 420
CGACTTCTCTCCTATCTCCTTTTACCTATGTTATGGATACGTAGTAAATTGACCGTGTATTACCTCC
L K E R I E E N G Y N T Y A S F N W Q H N G R
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
CAAATGTATGTGGCATTGAATGGAAGGAGCTCCAAGGAGAGGACAGAAAACGAAGGAAAAACACCT
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----| 490
GTTTACATACACGTAACCTTCTTCTCGAGGTTCTCTCCTGTCTTTGTGCTTCTTTTGTGGA
Q M Y V A L N G K G A P R R G Q K T R R K N T
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
CTGCTCACTTTCTTCCAATGGTGGTACACTCATAG
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----| 525
GACGAGTGAAGAAGGTTACCACCATGTGAGTATC
S A H F L P M V V H S
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|

FIG.24B

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ATGACCTGCCAGGCTCTGGGTCAGGACATGGTTTCTCCGGAAGCTACCAACTCTTCC
TCTTCCTCTTTCTCTTCCCCGTCTTCGCTGGTCGTACGTTTCGTTCTTACAACCAC
CTGCAGGGTGACGTTTCGTTGGCGTAACTGTTCTCTTTCACCAAATACTTCCTGAAA
ATCGAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCATC
CTGGAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAACAGCAAC
TATTACTTAGCCATGAACAAGAAGGGGAACTCTATGGCTCAAAAGAATTTAACAAT
GACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATCATTT
AACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCA
AGGAGAGGACAGAAAACACGAAGGAAAAACACCTCTGCTCACTTTCTTCCAATGGTG
GTACACTCATAG

MTCQALGQDMVSPEATNSSSSSFSSPSSAGRHVRSYNHLQGDVRWRKLFSTKYFLKIE
KNGKVSGETTKENCYPYSILEITSVEIGVVAVKAINSNYLAMNKKGKLYGSKEFNNDCKL
KERIEENGYNTYASFNWQHNGRQMYVALNGKGAPRRGQKTRRKNTSAHFLPMVHS.

FIG.25

ATGGCTGGTCGTACGTTTCGTTCTTACAACCACCTGCAGGGTGACGTTTCGTTGGCGT
AACTGTTCTCTTTCACCAAATACTTCCTGAAAATCGAAAAAACGGTAAAGTTTCT
GGGACCAAGAAGGAGAACTGCCCGTACAGCATCCTGGAGATAACATCAGTAGAAATC
GGAGTTGTTGCCGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGAAG
GGGAACTCTATGGCTCAAAAGAATTTAACAATGACTGTAAGCTGAAGGAGAGGATA
GAGGAAAATGGATACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGGCAA
ATGTATGTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGG
AAAAACACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAG

MAGRHVRSYNHLQGDVRWRKLFSTKYFLKIEKNGKVSGETTKENCYPYSILEITSVEIGV
VAVKAINSNYLAMNKKGKLYGSKEFNNDCKLKERIEENGYNTYASFNWQHNGRQMYVA
LNGKGAPRRGQKTRRKNTSAHFLPMVHS.

FIG.26

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ATGGTTCGTTGGCGTAACTGTTCTCTTTCACCAAATACTTCCTGAAAATCGAAAA
AACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCATCCTGGAGATA
ACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAAACAGCAACTATTACTTA
GCCATGAACAAGAAGGGGAACTCTATGGCTCAAAGAATTTAACAATGACTGTAAG
CTGAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATCATTTAACTGGCAG
CATAATGGGAGGCAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGA
CAGAAAACACGAAGGAAAAACACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCA
TAG

MVRWRKLFSTKYFLKIEKNGKVSgtkkENCPYSILEITSVEIGVVAVKAINSnyyLAM
NKKGKLYGSKEFNNDCKLKERIEENGYNTYASFNWQHNGRQMYVALNGKGAPRRGQKTR
RKNTSAHFLPMVVHS.

FIG.27

ATGGAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCAT
CCTGGAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAAACAGCA
ACTATTACTTAGCCATGAACAAGAAGGGGAACTCTATGGCTCAAAGAATTTAAC
AATGACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATC
ATTTAACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTGAATGGAAAAGGAG
CTCCAAGGAGAGGACAGAAAACACGAAGGAAAAACACCTCTGCTCACTTTCTTCCA
ATGGTGGTACACTCATAG

MEKNGKVSgtkkENCPYSILEITSVEIGVVAVKAINSnyyLAMNKKGKLYGSKEFNNDCK
LKERIEENGYNTYASFNWQHNGRQMYVALNGKGAPRRGQKTRRKNTSAHFLPMVVH
S.

FIG.28

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ATGGAGAACTGCCCCGTACAGCATCCTGGAGATAACATCAGTAGAAATCGGAGTTGT
TGCCGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGAAGGGGAAAC
TCTATGGCTCAAAGAATTTAACAATGACTGTAAGCTGAAGGAGAGGATAGAGGAA
AATGGATACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGGCAAATGTA
TGTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGGAAAA
ACACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAG

MENCPSYLEITSVEIGVVAVKAINSNYLAMNKKGKLYGSKEFNNDCKLKERIEENGY
NTYASFNWQHNGRQMYVALNGKGAPRRGQKTRRKNTSAHFLPMVVHS.

FIG.29

ATGGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGAAGGGGAACT
CTATGGCTCAAAGAATTTAACAATGACTGTAAGCTGAAGGAGAGGATAGAGGAAA
ATGGATACAATACCTATGCATCATTTAACTGGCAGCATAATGGGAGGCAAATGTAT
GTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACACGAAGGAAAA
CACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAG

MVKAINSNYLAMNKKGKLYGSKEFNNDCKLKERIEENGYNTYASFNWQHNGRQMY
VALNGKGAPRRGQKTRRKNTSAHFLPMVVHS.

FIG.30

ATGGGGAACTCTATGGCTCAAAGAATTTAACAATGACTGTAAGCTGAAGGAGAG
GATAGAGGAAAATGGATACAATACCTATGCATCATTTAACTGGCAGCATAATGGGA
GGCAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCAAGGAGAGGACAGAAAACA
CGAAGGAAAAACACCTCTGCTCACTTTCTTCCAATGGTGGTACACTCATAG

MGKLYGSKEFNNDCKLKERIEENGYNTYASFNWQHNGRQMYVALNGKGAPRRGQK
RRKNTSAHFLPMVVHS.

FIG.31

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ATGACCTGCCAGGCTCTGGGTCAGGACATGGTTTCTCCGGAAGCTACCAACTCTTCC
TCTTCCTCTTTCTTTCCCGTCTTCCGCTGGTCGTACGTTTCGTTCTTACAACCAC
CTGCAGGGTGACGTTGTTGGCGTAAACTGTTCTTTTACCAAATACTTCCTGAAA
ATCGAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCATC
CTGGAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAACAGCAAC
TATTACTTAGCCATGAACAAGAAGGGGAAACTCTATGGCTCAAAGAATTTAACAAT
GACTGTAAGCTGAAG

MTCQALGQDMVSPEATNSSSSSFSSPSSAGRHVRSYNHLQGDVWRKLFSTKYFLKIE
KNGKVSgtkkENCPYSILEITSVEIGVVAVKAINSYYLAMNKKGKLYGSKEFNNDCKL
K

FIG.32

ATGGCTGGTCGTACGTTTCGTTCTTACAACCACCTGCAGGGTGACGTTTCGTTGGCGT
AAACTGTTCTTTTACCAAATACTTCCTGAAAATCGAAAAAACGGTAAAGTTTCT
GGGACCAAGAAGGAGAACTGCCCGTACAGCATCCTGGAGATAACATCAGTAGAAATC
GGAGTTGTTGCCGTCAAAGCCATTAACAGCAACTATTACTTAGCCATGAACAAGAAG
GGGAAACTCTATGGCTCAAAGAATTTAACAATGACTGTAAGCTGAAG

MAGRHVRSYNHLQGDVWRKLFSTKYFLKIEKNGKVSgtkkENCPYSILEITSVEIGV
VAVKAINSYYLAMNKKGKLYGSKEFNNDCKLK

FIG.33

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C-37 To Ser

ATGACCTCTCAGGCTCTGGGTCAGGACATGGTTTCTCCGGAAGCTACCAACTCTTCC
TCTTCCTCTTTCTCTTCCCGTCTTCCGCTGGTCGTCACGTTTCGTTCTTACAACCAC
CTGCAGGGTGACGTTTCGTTGGCGTAACTGTTCTCTTTCACCAAATACTTCCTGAAA
ATCGAAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTGCCCGTACAGCATC
CTGGAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAAACAGCAAC
TATTACTTAGCCATGAACAAGAAGGGGAAACTCTATGGCTCAAAAGAATTTAACAAT
GACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATCATTT
AACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCA
AGGAGAGGACAGAAAACACGAAGGAAAAACACCTCTGCTCACTTTCTTCCAATGGTG
GTACACTCATAG

FIG.34

C-106 To Ser

ATGACCTGCCAGGCTCTGGGTCAGGACATGGTTTCTCCGGAAGCTACCAACTCTTCC
TCTTCCTCTTTCTCTTCCCGTCTTCCGCTGGTCGTCACGTTTCGTTCTTACAACCAC
CTGCAGGGTGACGTTTCGTTGGCGTAACTGTTCTCTTTCACCAAATACTTCCTGAAA
ATCGAAAAAAACGGTAAAGTTTCTGGGACCAAGAAGGAGAACTCTCCGTACAGCATC
CTGGAGATAACATCAGTAGAAATCGGAGTTGTTGCCGTCAAAGCCATTAAACAGCAAC
TATTACTTAGCCATGAACAAGAAGGGGAAACTCTATGGCTCAAAAGAATTTAACAAT
GACTGTAAGCTGAAGGAGAGGATAGAGGAAAATGGATACAATACCTATGCATCATTT
AACTGGCAGCATAATGGGAGGCAAATGTATGTGGCATTGAATGGAAAAGGAGCTCCA
AGGAGAGGACAGAAAACACGAAGGAAAAACACCTCTGCTCACTTTCTTCCAATGGTG
GTACACTCATAG

FIG.35

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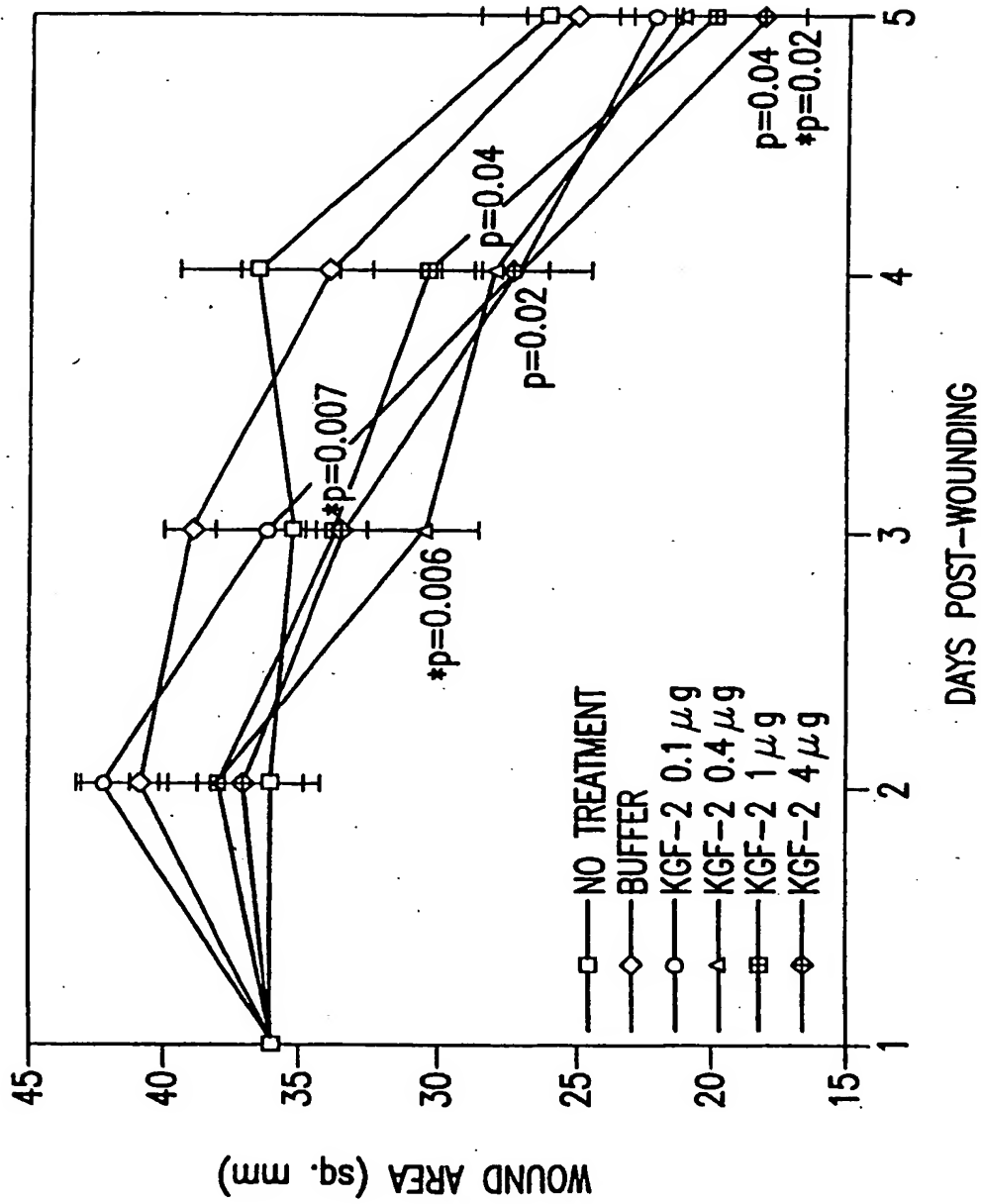


FIG.36

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EFFECT OF KGF-2 $\Delta 33$ ON NORMAL WOUND HEALING RAT MODEL

TREATMENT GROUPS	WOUND SIZE (mm)	% WOUND CLOSURE	HISTOLOGICAL SCORE	RE-EPITH. (μm)	BrdU SCORE
NO TREATMENT	25.9 \pm 2.5	58.8 \pm 3.7	6.8 \pm 0.2	1142 \pm 141	3.8 \pm 0.4
BUFFER	25.1 \pm 1.7	60.2 \pm 2.6	6.4 \pm 0.2	923 \pm 61	5.0 \pm 0.4
KGF-2/ $\Delta 33$ (0.1 μg)	22.0 \pm 0.9	65 \pm 1.4	6.8 \pm 0.2	1275 \pm 148	4.6 \pm 0.7
KGF-2/ $\Delta 33$ (0.4 μg)	21.1 \pm 1.4	68.4 \pm 2.4	8.0 \pm 0.5 p=0.0445*	1310 \pm 182	4.2 \pm 0.7
KGF-2/ $\Delta 33$ (1.0 μg)	19.9 \pm 1.5	66.2 \pm 2.1	8.4 \pm 0.4 p=0.0159* p=0.0053†	1389 \pm 115 p=0.0074†	3.3 \pm 0.25 p=0.0217†
KGF-2/ $\Delta 33$ (4.0 μg)	18.1 \pm 1.6 p=0.0398* p=0.0200†	71.2 \pm 2.6 p=0.0367* p=0.0217†	8.5 \pm 0.3 p=0.0047* p=0.0445†	1220 \pm 89 p=0.0254†	5.3 \pm 0.9

FIG. 37

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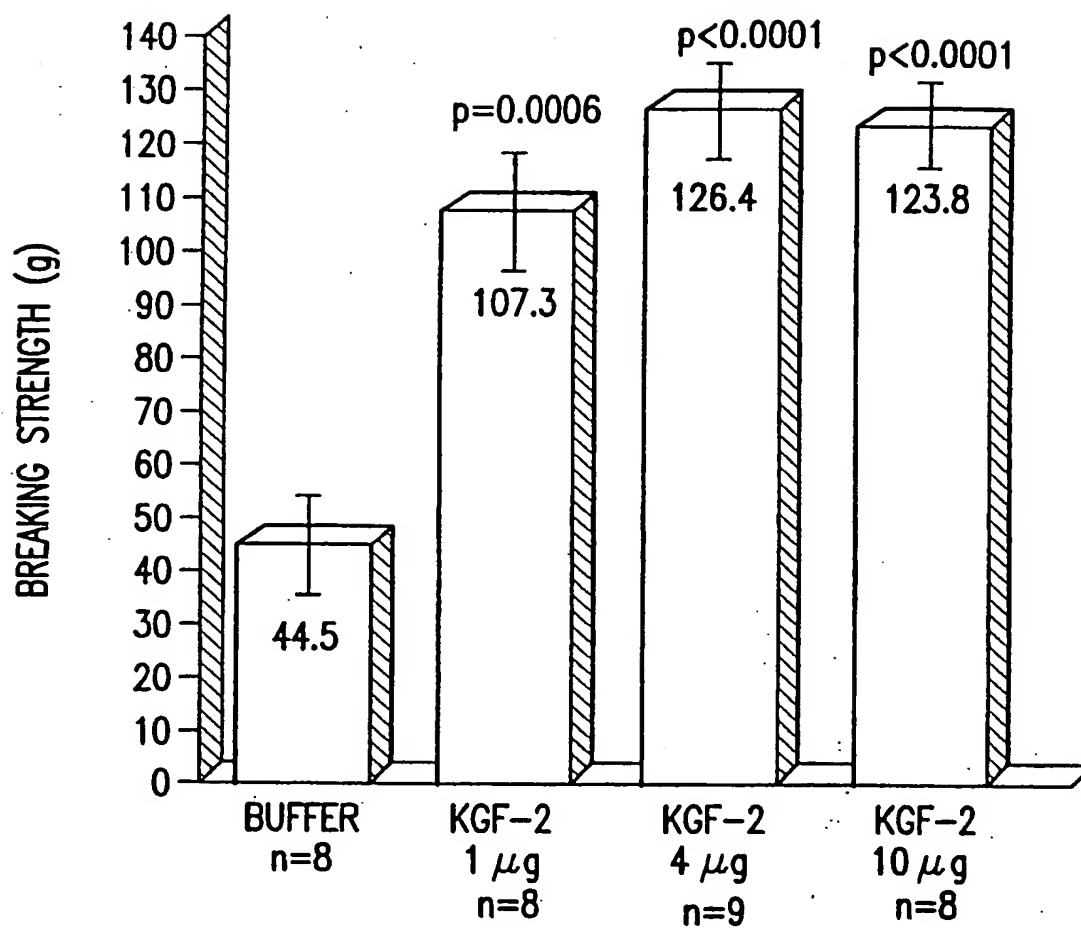


FIG.38

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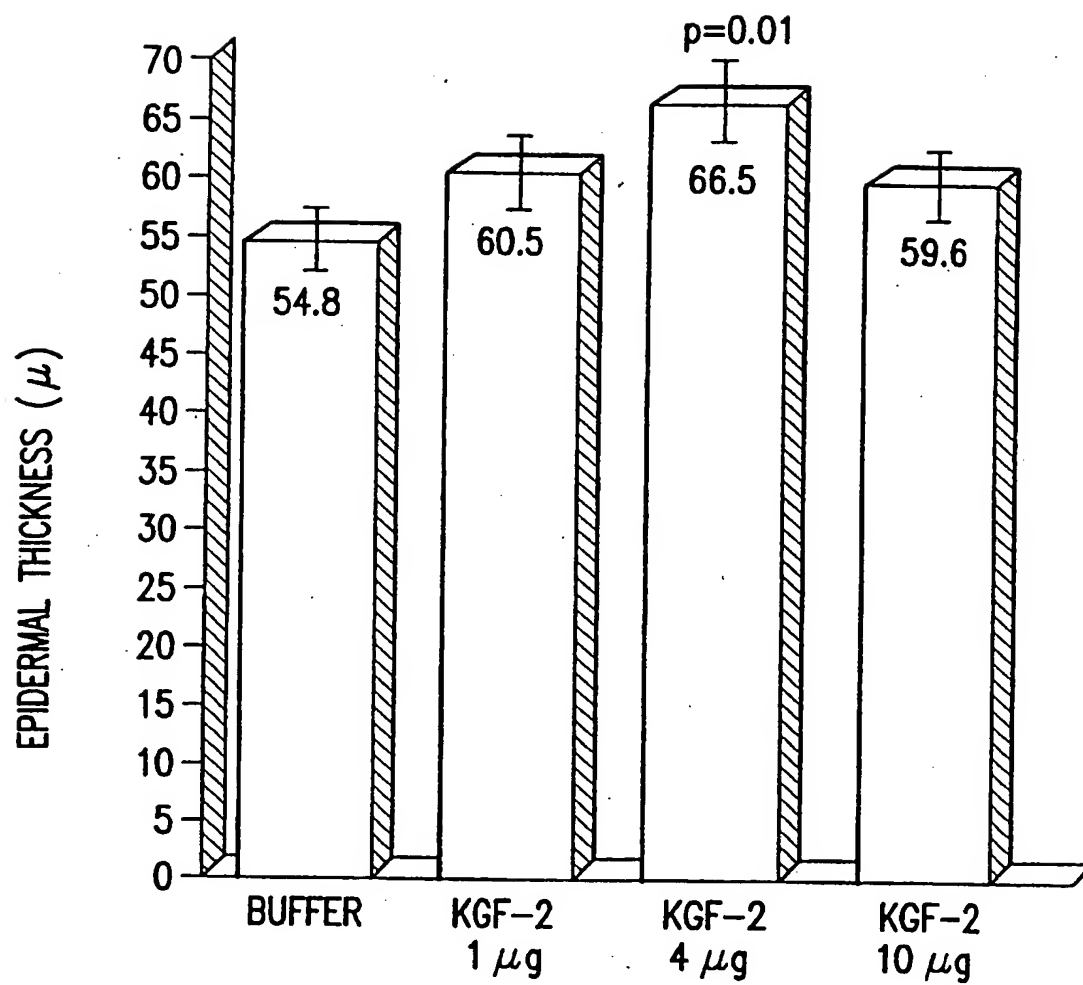


FIG.39

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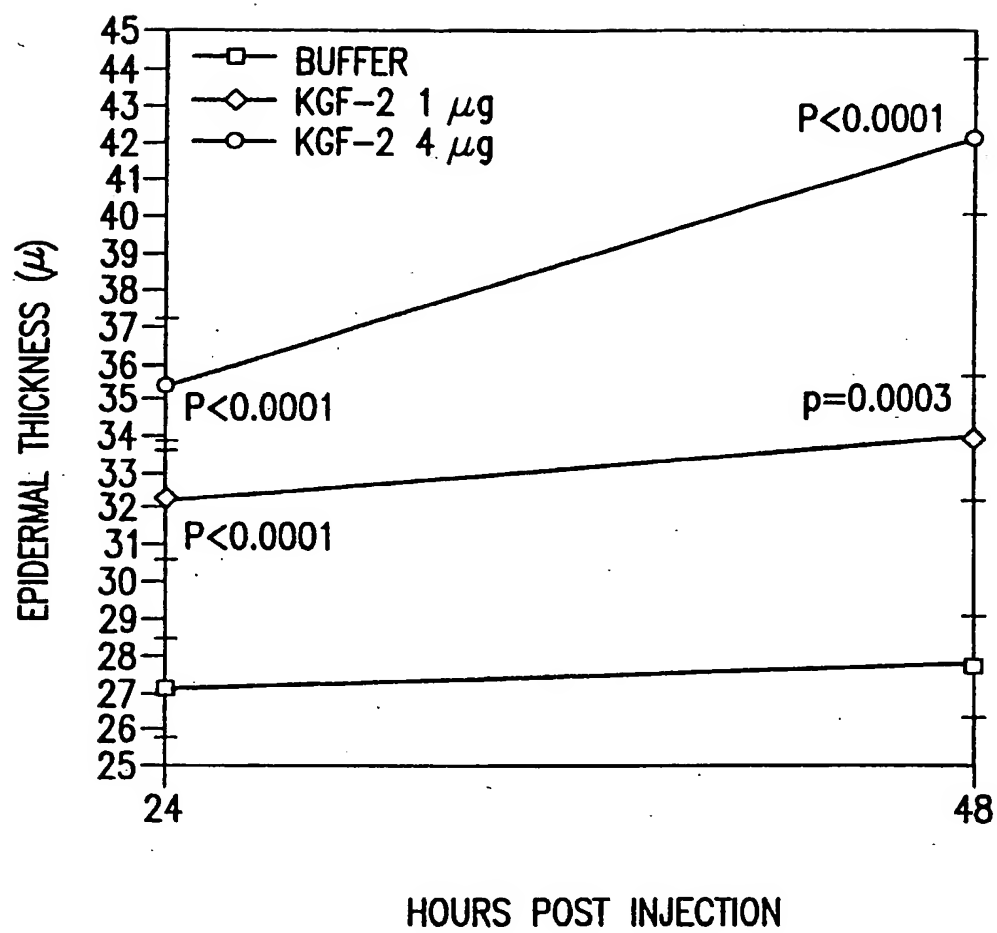


FIG.40

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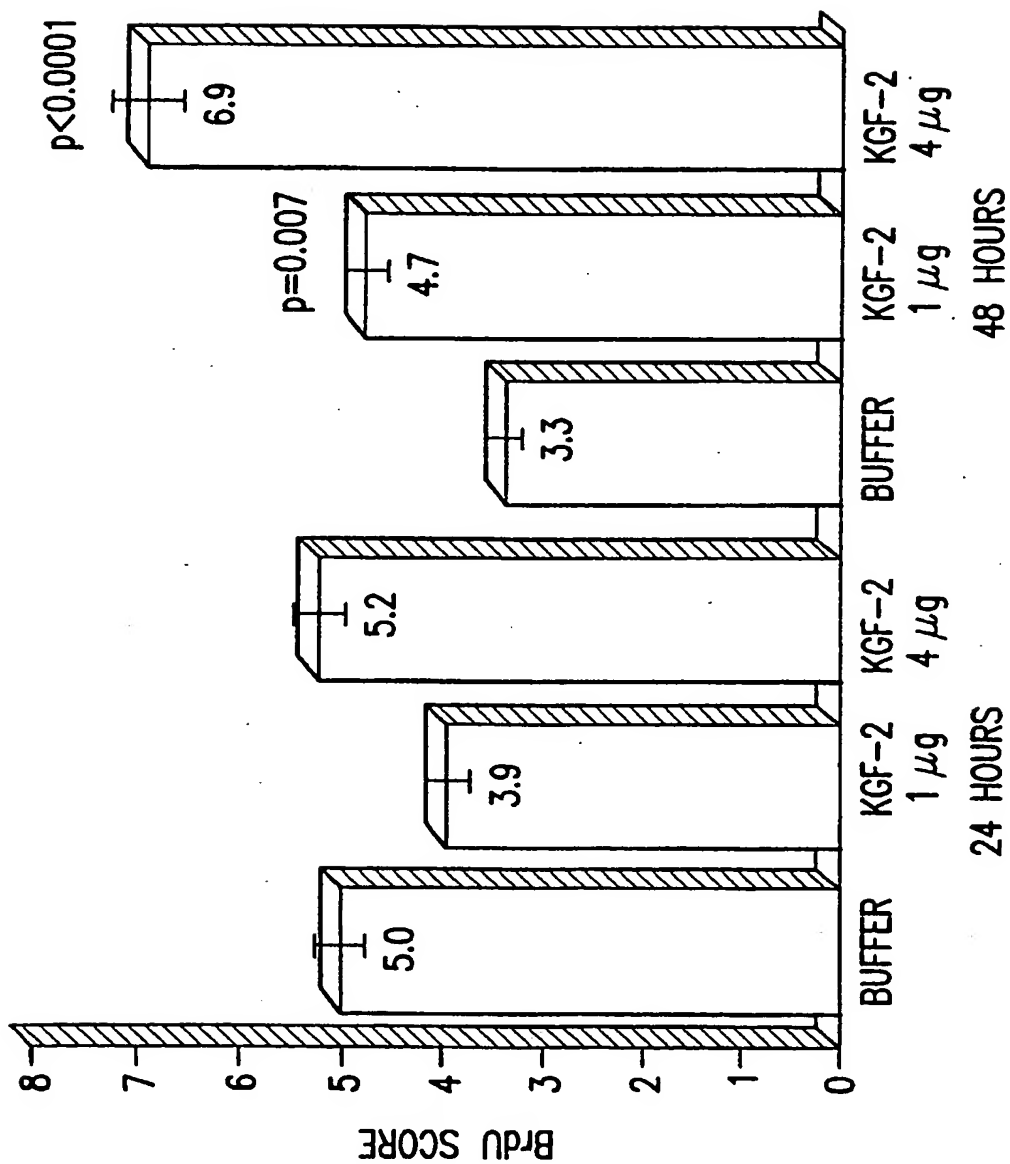


FIG.41

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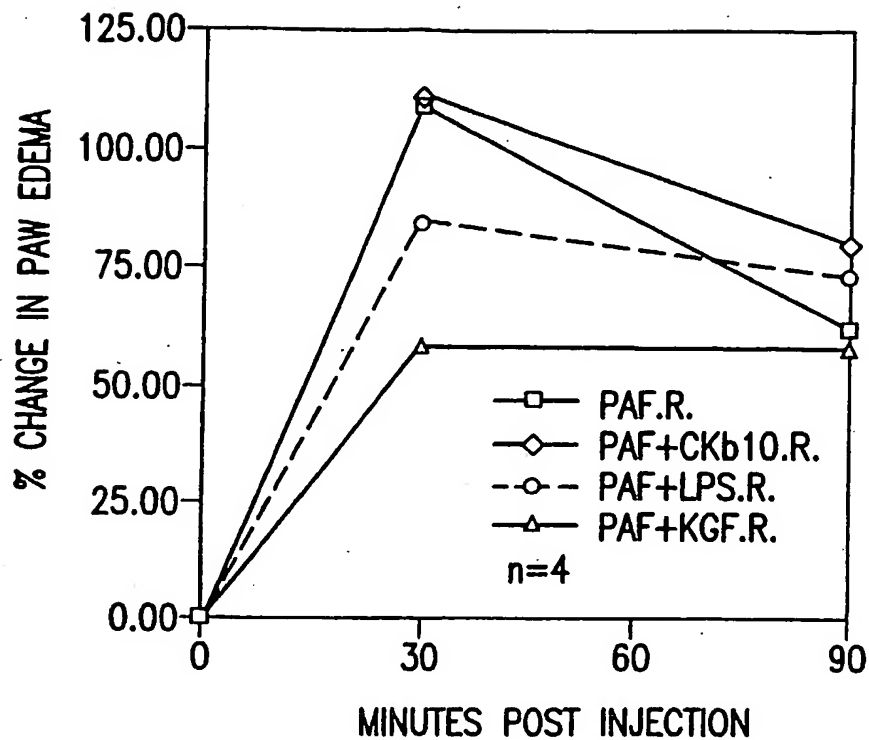


FIG.42A

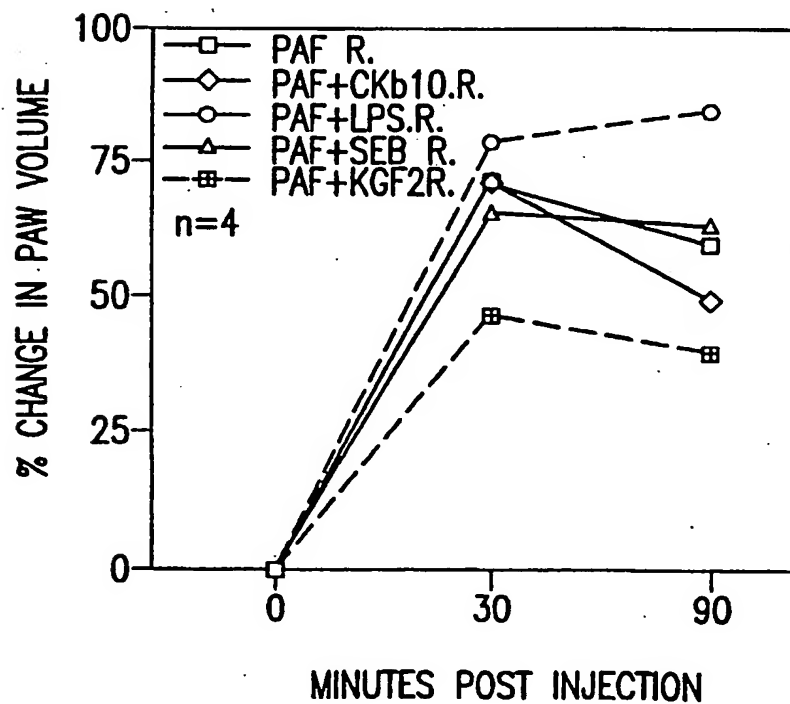


FIG.42B

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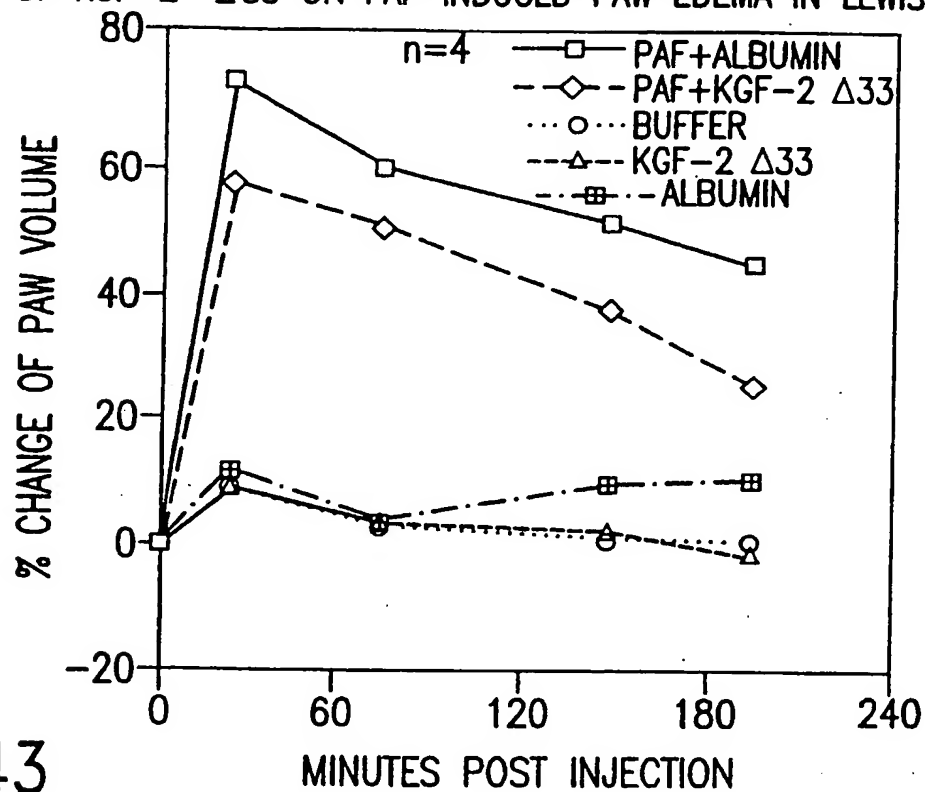
EFFECT OF KGF-2 $\Delta 33$ ON PAF-INDUCED PAW EDEMA IN LEWIS RATS

FIG.43

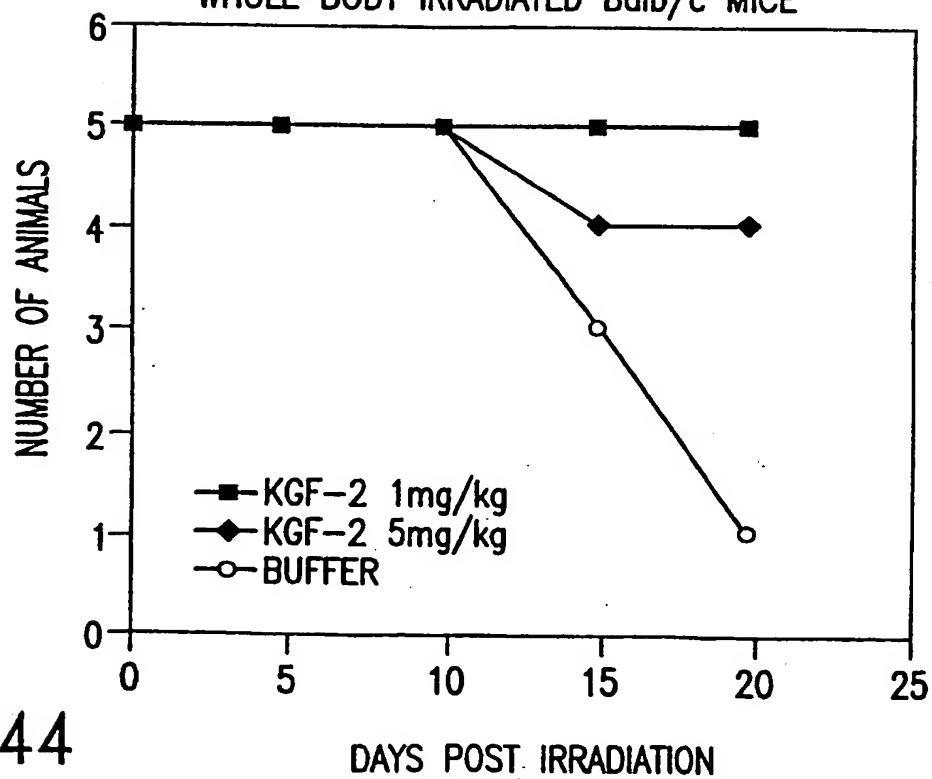
EFFECT OF KGF-2 $\Delta 33$ ON SURVIVAL OF WHOLE BODY IRRADIATED Balb/c MICE

FIG.44

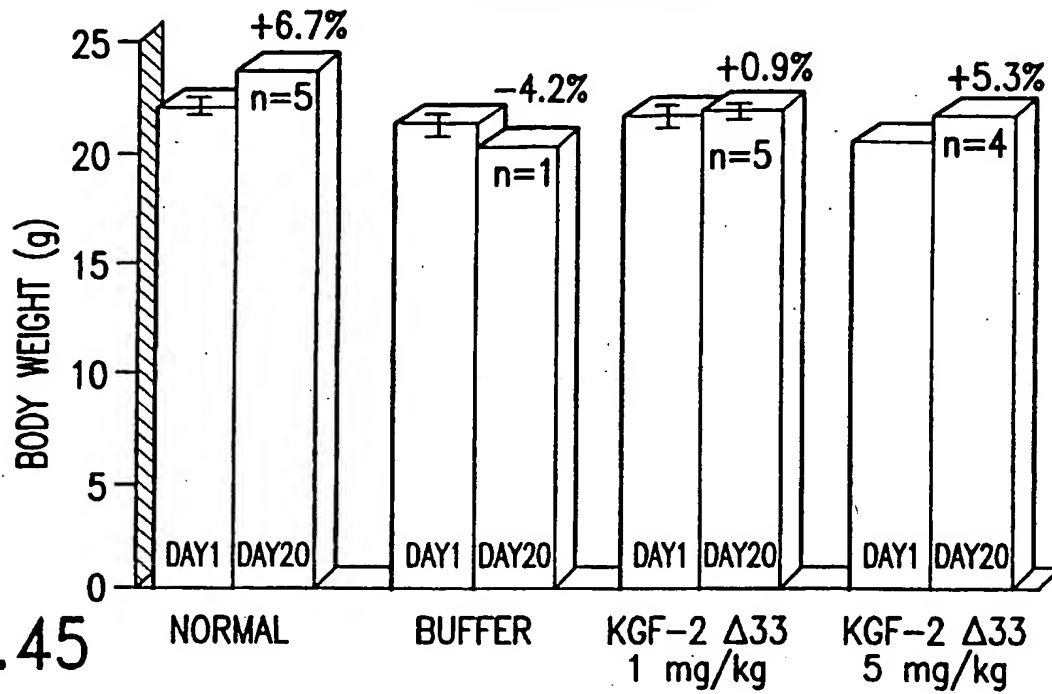
EFFECT OF KGF-2 $\Delta 33$ ON BODY WEIGHT OF IRRADIATED MICE 54/64

FIG.45

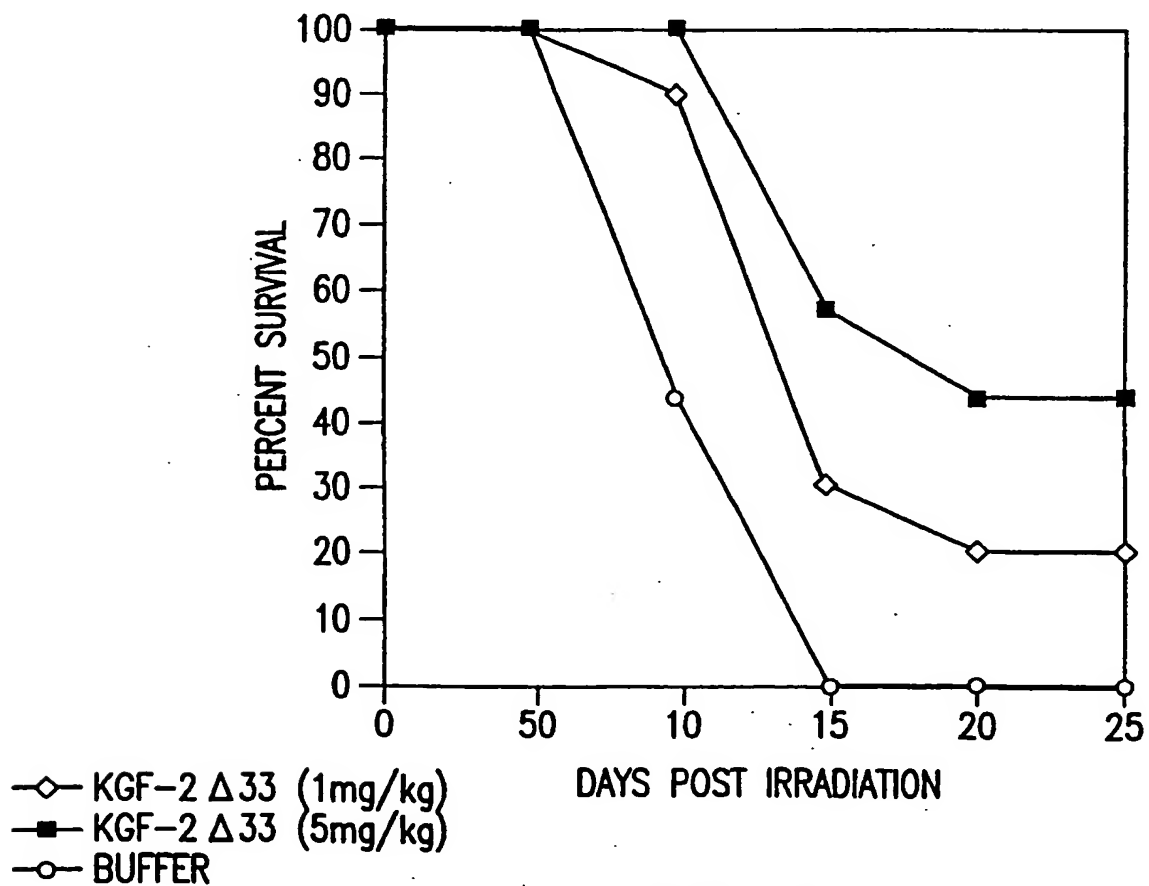


FIG.46

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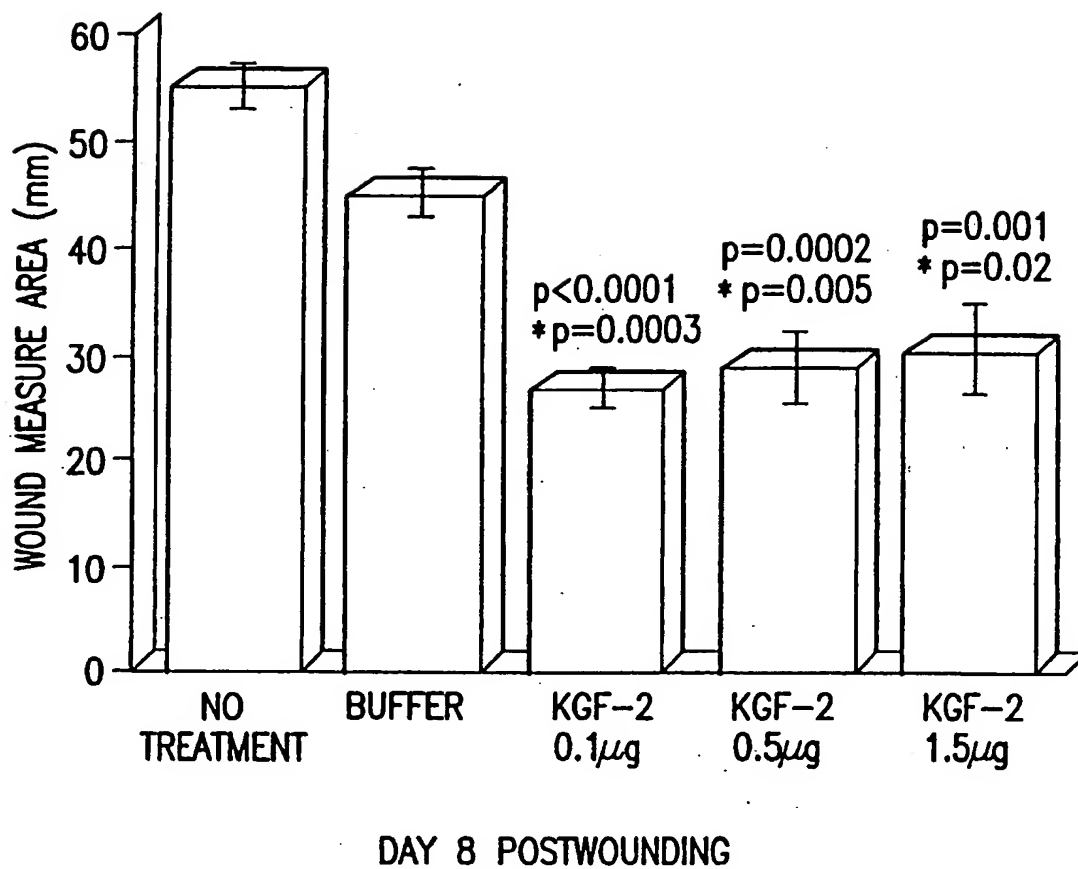


FIG.47

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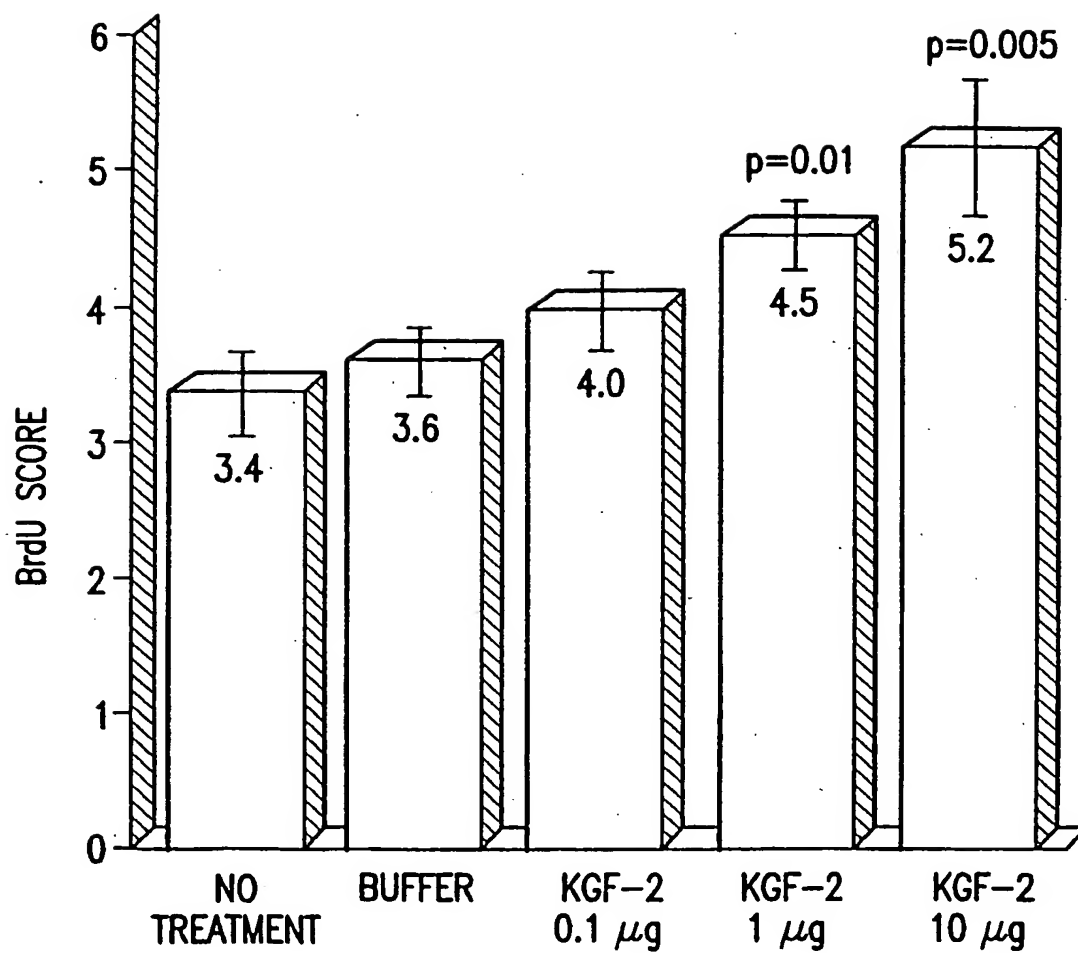


FIG.48

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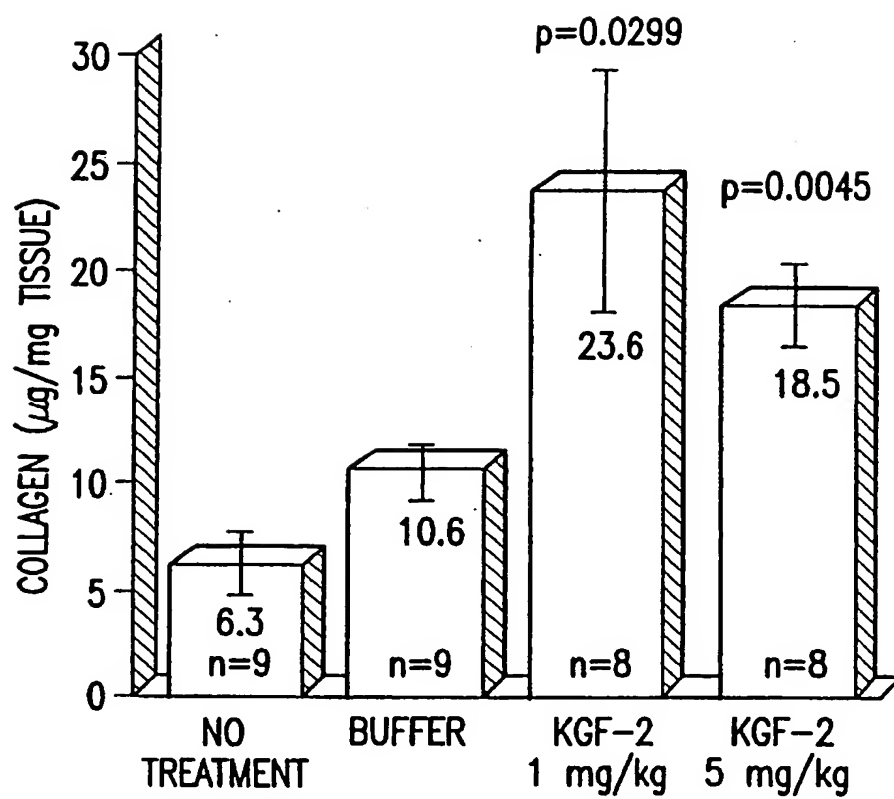


FIG.49

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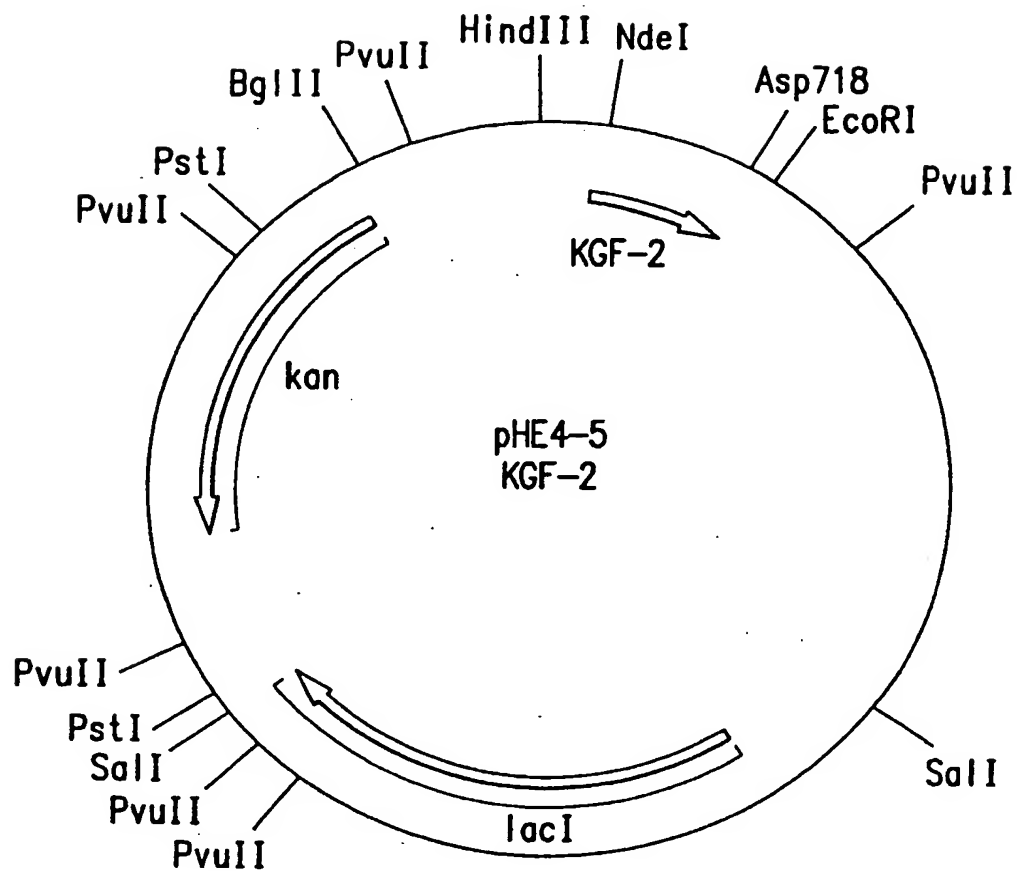


FIG. 50

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1 AAGCTTAAAAAACTGCAAAAAATAGT ⁻³⁵ TTGACT ^{Operator 1} TGTGAGCGGATAACAAT

50 ⁻¹⁰ TAAGAT GTACCCA ^{Operator 2} ATTGTGAGCGGATAACAAT TTCACACATTAA

94 ^{S/D} AGAGGAG AAATTA CATATG

FIG. 51

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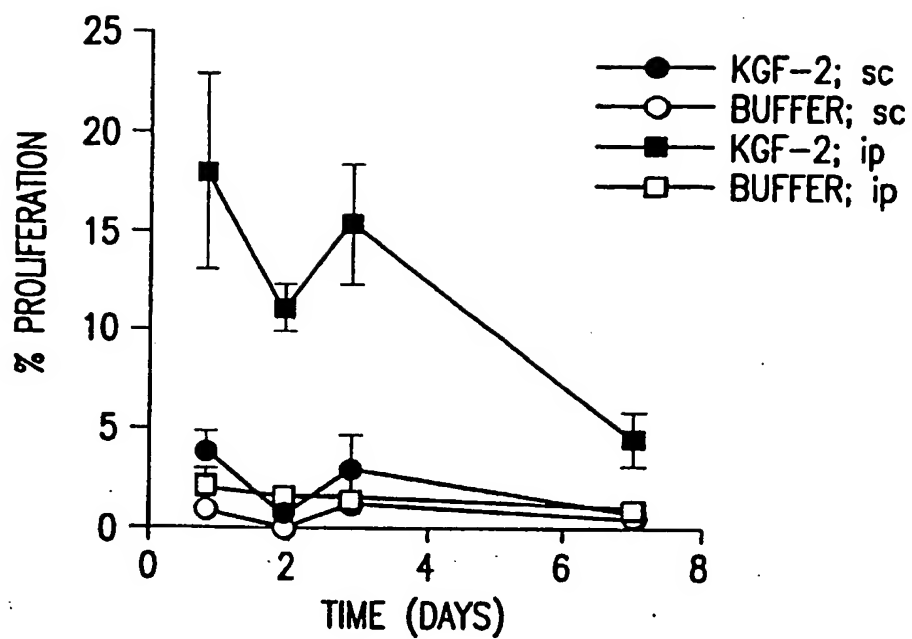


FIG. 52

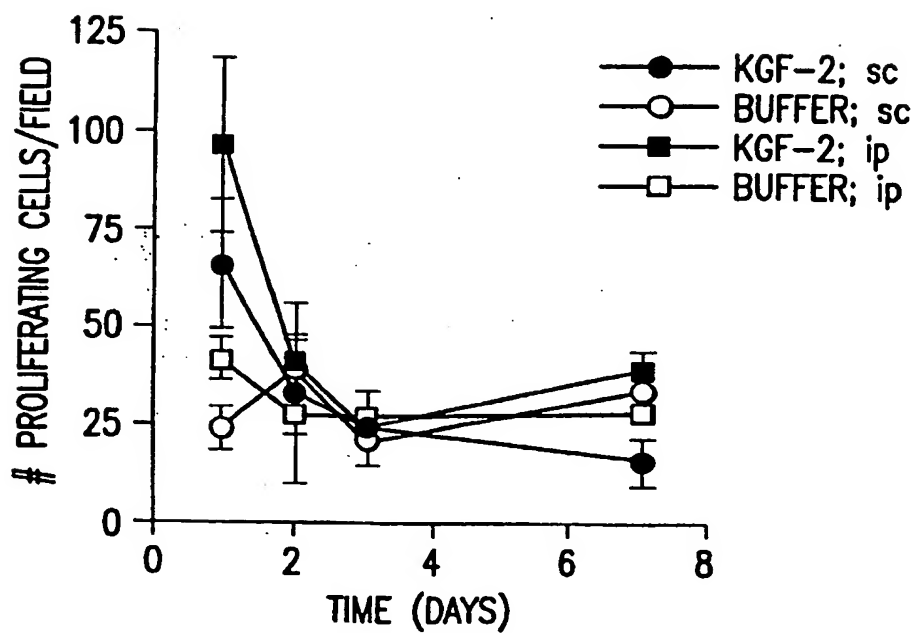


FIG. 53

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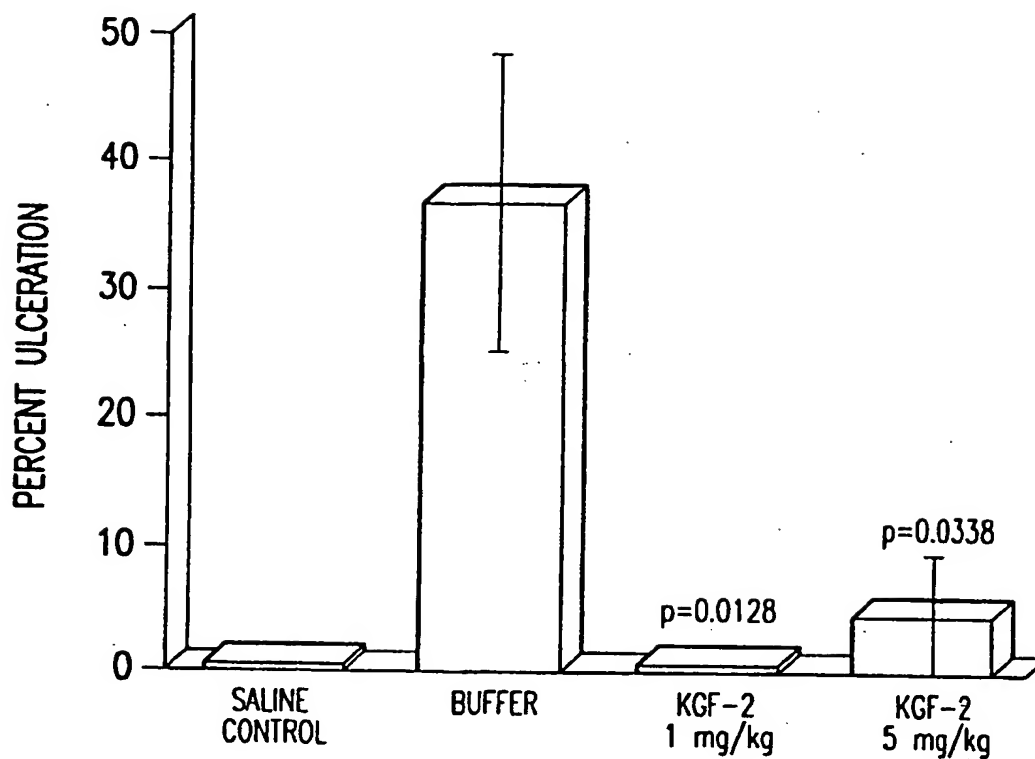


FIG. 54

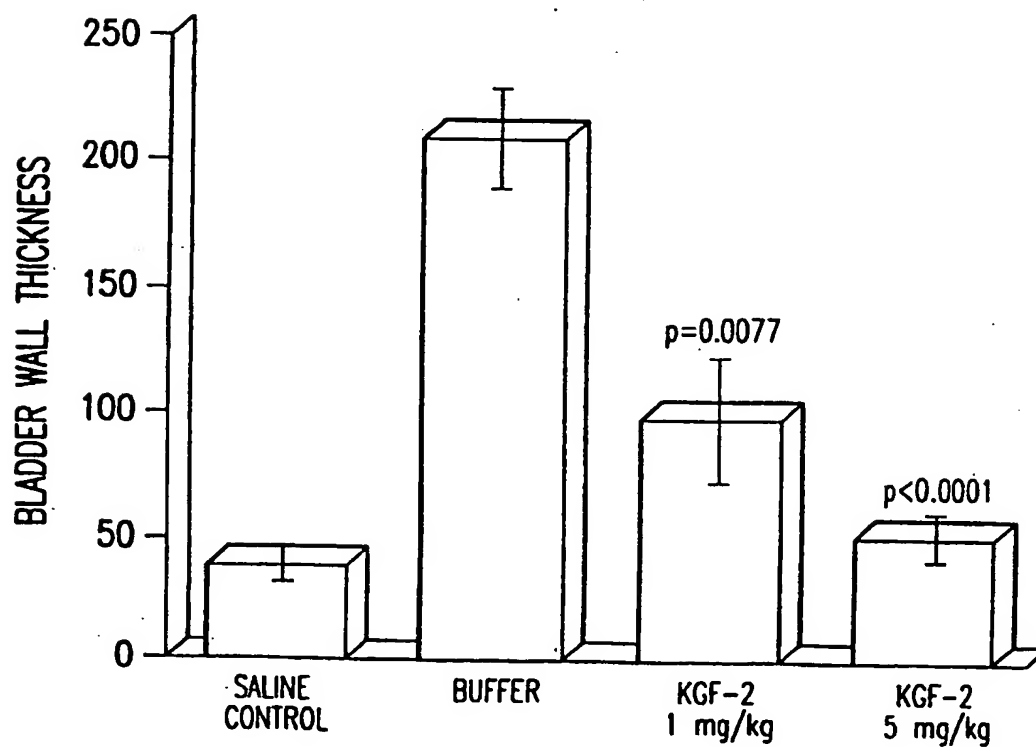


FIG. 55

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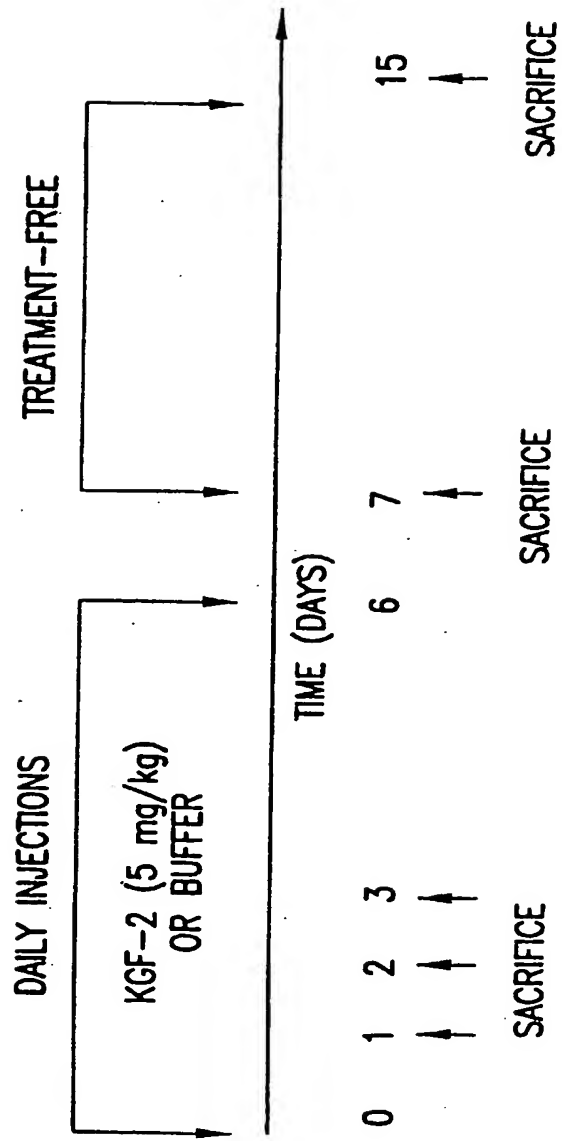


FIG. 56

PROLIFERATION OF HEPATOCYTES FOLLOWING SYSTEMIC ADMINISTRATION OF KGF-2

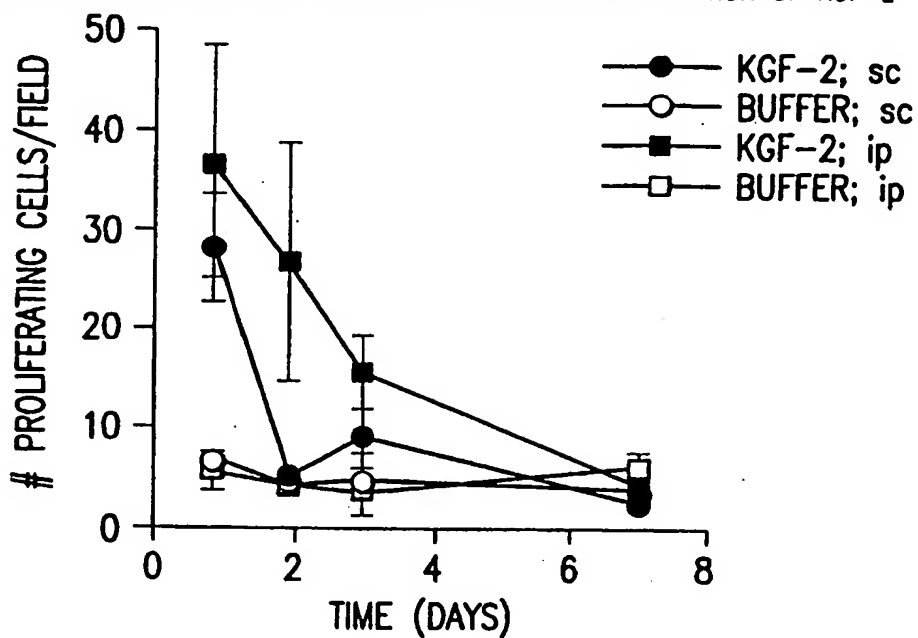


FIG. 57

PROLIFERATION OF PANCREATIC CELLS FOLLOWING SYSTEMIC ADMINISTRATION OF KGF-2

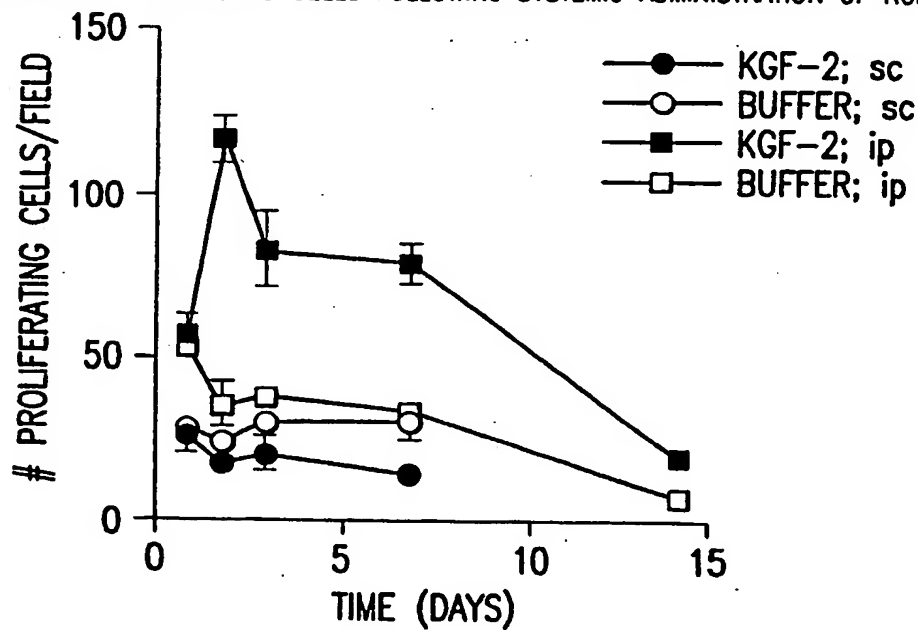


FIG. 58

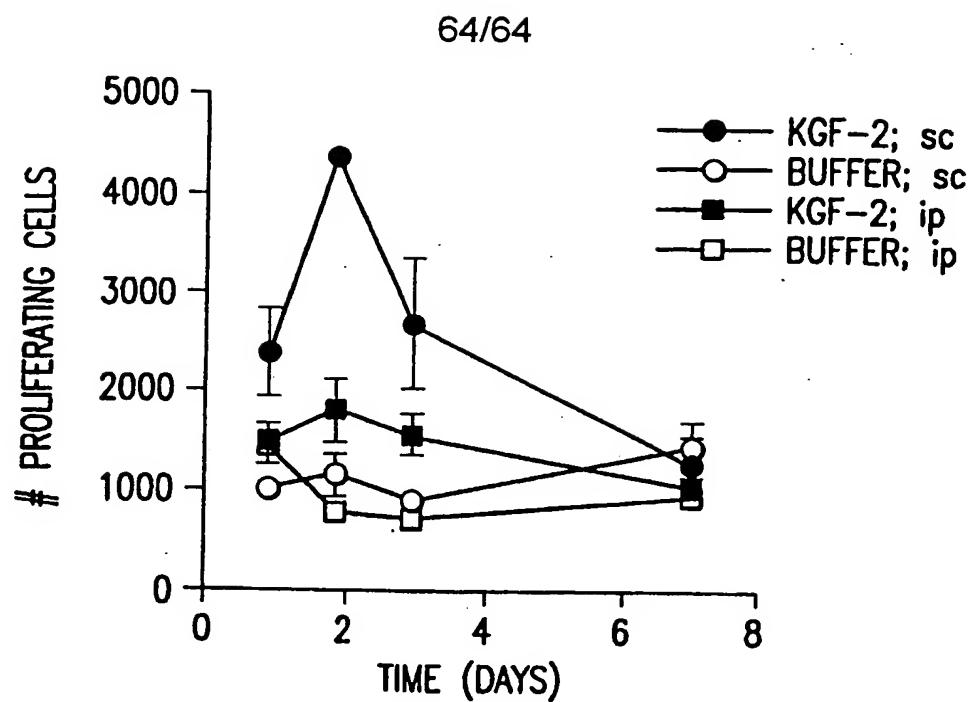


FIG. 59

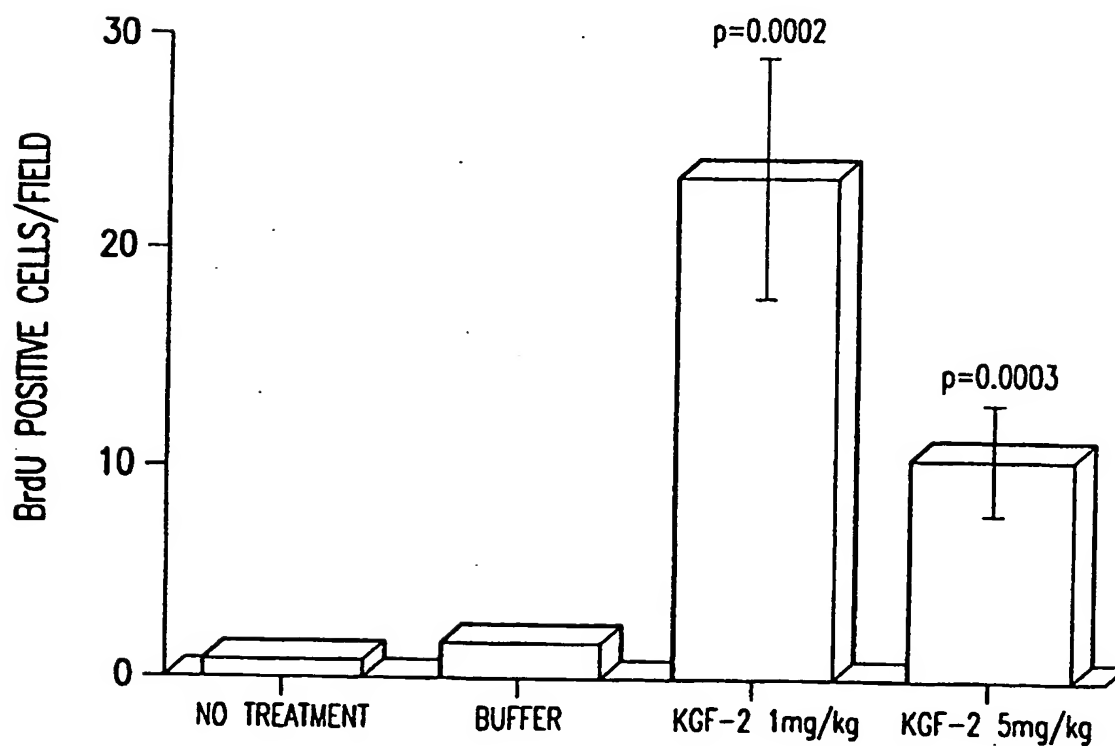


FIG. 60

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SEQUENCE LISTING

<110> Ruben, Steven M.
 Jimenez, Pablo
 Duan, D. Roxanne
 Rampy, Mark A.
 Mendrick, Donna
 Zhang, Jun
 Ni, Jian
 Moore, Paul A.
 Coleman, Timothy A.
 Gruber, Joachim R.
 Dillon, Patrick J.
 Gentz, Reiner L.

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 <151> 2001-01-05

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 <151> 2001-11-09

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<170> PatentIn Ver. 2.1

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 1 5 10 15
 ccc ggc tgc tgc tgc tgc tgc ttt ttg ttg ctg ttc ttg gtg tct tcc 96
 Pro Gly Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser
 20 25 30
 gtc cct gtc acc tgc caa gcc ctt ggt cag gac atg gtg tca cca gag 144
 Val Pro Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu
 35 40 45
 gcc acc aac tct tct tcc tcc tcc ttc tcc tct cct tcc agc gcg gga 192
 Ala Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly

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50	55	60	
agg cat gtg cgg agc tac aat cac ctt caa gga gat gtc cgc tgg aga			240
Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg			
65	70	75	80
aag cta ttc tct ttc acc aag tac ttt ctc aag att gag aag aac ggg			288
Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly			
	85	90	95
aag gtc agc ggg acc aag aag gag aac tgc ccg tac agc atc ctg gag			336
Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu			
	100	105	110
ata aca tca gta gaa atc gga gtt gtt gcc gtc aaa gcc att aac agc			384
Ile Thr Val Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser			
	115	120	125
aac tat tac tta gcc atg aac aag aag ggg aaa ctc tat ggc tca aaa			432
Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys			
	130	135	140
gaa ttt aac aat gac tgt aag ctg aag gag agg ata gag gaa aat gga			480
Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly			
	145	150	155
tac aat acc tat gca tca ttt aac tgg cag cat aat ggg agg caa atg			528
Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met			
	165	170	175
tat gtg gca ttg aat gga aaa gga gct cca agg aga gga cag aaa aca			576
Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr			
	180	185	190
cga agg aaa aac acc tct gct cac ttt ctt cca atg gtg gta cac tca			624
Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser			
	195	200	205
tag			627
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Pro Gly Cys Cys Cys Cys Cys Phe Leu Leu Phe Leu Val Ser Ser			
	20	25	30
Val Pro Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu			
	35	40	45
Ala Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly			
	50	55	60
Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg			
65	70	75	80

Lys	Leu	Phe	Ser	Phe 85	Thr	Lys	Tyr	Phe	Leu 90	Lys	Ile	Glu	Lys	Asn 95	Gly
Lys	Val	Ser	Gly 100	Thr	Lys	Lys	Glu	Asn 105	Cys	Pro	Tyr	Ser	Ile 110	Leu	Glu
Ile	Thr	Ser 115	Val	Glu	Ile	Gly	Val 120	Val	Ala	Val	Lys	Ala 125	Ile	Asn	Ser
Asn	Tyr 130	Tyr	Leu	Ala	Met	Asn 135	Lys	Lys	Gly	Lys	Leu 140	Tyr	Gly	Ser	Lys
Glu 145	Phe	Asn	Asn	Asp	Cys 150	Lys	Leu	Lys	Glu	Arg 155	Ile	Glu	Glu	Asn	Gly 160
Tyr	Asn	Thr	Tyr	Ala 165	Ser	Phe	Asn	Trp	Gln 170	His	Asn	Gly	Arg	Gln 175	Met
Tyr	Val	Ala	Leu 180	Asn	Gly	Lys	Gly	Ala 185	Pro	Arg	Arg	Gly	Gln 190	Lys	Thr
Arg	Arg	Lys 195	Asn	Thr	Ser	Ala	His 200	Phe	Leu	Pro	Met	Val 205	Val	His	Ser

. 36

35

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catgccatgg cgtgccaaagc ccttggtcag gacatg 36

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<213> Artificial Sequence

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oligonucleotide

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oligonucleotide

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gcgggatccg ccatcatgtg gaaatggata ctcac 35

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<213> Artificial Sequence

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oligonucleotide

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gcgcggtacc acaaacgttg ccttcct 27

<210> 9
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<213> Artificial Sequence

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<223> Description of Artificial Sequence:
oligonucleotide

<400> 9
taacgaggat cgcctcatcat gtggaaatgg atactgacac 40

<210> 10
<211> 38
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<213> Artificial Sequence

<220>
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-5-

oligonucleotide

<400> 10
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<213> Artificial Sequence

<220>
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oligonucleotide

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attaaccctc actaaagggga ggccatgtgg aaatggatac tgacacattg tgcc 54

<210> 12
<211> 35
<212> DNA
<213> Artificial Sequence

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oligonucleotide

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<211> 206
<212> PRT
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Met Ser Gly Pro Gly Thr Ala Ala Val Ala Leu Leu Pro Ala Val Leu
1 5 10 15
Leu Ala Leu Leu Ala Pro Trp Ala Gly Arg Gly Gly Ala Ala Ala Pro
20 25 30
Thr Ala Pro Asn Gly Thr Leu Glu Ala Glu Leu Glu Arg Arg Trp Glu
35 40 45
Ser Leu Val Ala Leu Ser Leu Ala Arg Leu Pro Val Ala Ala Gln Pro
50 55 60
Lys Glu Ala Ala Val Gln Ser Gly Ala Gly Asp Tyr Leu Leu Gly Ile
65 70 75 80
Lys Arg Leu Arg Arg Leu Tyr Cys Asn Val Gly Ile Gly Phe His Leu
85 90 95
Gln Ala Leu Pro Asp Gly Arg Ile Gly Gly Ala His Ala Asp Thr Arg
100 105 110
Asp Ser Leu Leu Glu Leu Ser Pro Val Glu Arg Gly Val Val Ser Ile
115 120 125

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Phe Gly Val Ala Ser Arg Phe Phe Val Ala Met Ser Ser Lys Gly Lys
 130 135 140

Leu Tyr Gly Ser Pro Phe Phe Thr Asp Glu Cys Thr Phe Lys Glu Ile
 145 150 155 160

Leu Leu Pro Asn Asn Tyr Asn Ala Tyr Glu Ser Tyr Lys Tyr Pro Gly
 165 170 175

Met Phe Ile Ala Leu Ser Lys Asn Gly Lys Thr Lys Lys Gly Asn Arg
 180 185 190

Val Ser Pro Thr Met Lys Val Thr His Phe Leu Pro Arg Leu
 195 200 205

<210> 14

<211> 198

<212> PRT

<213> Homo sapiens.

<400> 14

Met Ser Arg Gly Ala Gly Arg Leu Gln Gly Thr Leu Trp Ala Leu Val
 1 5 10 15

Phe Leu Gly Ile Leu Val Gly Met Val Val Pro Ser Pro Ala Gly Thr
 20 25 30

Arg Ala Asn Asn Thr Leu Leu Asp Ser Arg Gly Trp Gly Thr Leu Leu
 35 40 45

Ser Arg Ser Arg Ala Gly Leu Ala Gly Glu Ile Ala Gly Val Asn Trp
 50 55 60

Glu Ser Gly Tyr Leu Val Gly Ile Lys Arg Gln Arg Arg Leu Tyr Cys
 65 70 75 80

Asn Val Gly Ile Gly Phe His Leu Gln Val Leu Pro Asp Gly Arg Ile
 85 90 95

Ser Gly Thr His Glu Glu Asn Pro Tyr Ser Leu Leu Glu Ile Ser Thr
 100 105 110

Val Glu Arg Gly Val Val Ser Leu Phe Gly Val Arg Ser Ala Leu Phe
 115 120 125

Val Ala Met Asn Ser Lys Gly Arg Leu Tyr Ala Thr Pro Ser Phe Gln
 130 135 140

Glu Glu Cys Lys Phe Arg Glu Thr Leu Leu Pro Asn Asn Tyr Asn Ala
 145 150 155 160

Tyr Glu Ser Asp Leu Tyr Gln Gly Thr Tyr Ile Ala Leu Ser Lys Tyr
 165 170 175

Gly Arg Val Lys Arg Gly Ser Lys Val Ser Pro Ile Met Thr Val Thr
 180 185 190

His Phe Leu Pro Arg Ile
 195

-7-

<210> 15
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 Ser Ala Trp Ala His Gly Glu Lys Arg Leu Ala Pro Lys Gly Gln Pro
 20 25 30
 Gly Pro Ala Ala Thr Asp Arg Asn Pro Arg Gly Ser Ser Ser Arg Gln
 35 40 45
 Ser Ser Ser Ser Ala Met Ser Ser Ser Ser Ala Ser Ser Ser Pro Ala
 50 55 60
 Ala Ser Leu Gly Ser Gln Gly Ser Gly Leu Glu Gln Ser Ser Phe Gln
 65 70 75 80
 Trp Ser Pro Ser Gly Arg Arg Thr Gly Ser Leu Tyr Cys Arg Val Gly
 85 90 95
 Ile Gly Phe His Leu Gln Ile Tyr Pro Asp Gly Lys Val Asn Gly Ser
 100 105 110
 His Glu Ala Asn Met Leu Ser Val Leu Glu Ile Phe Ala Val Ser Gln
 115 120 125
 Gly Ile Val Gly Ile Arg Gly Val Phe Ser Asn Lys Phe Leu Ala Met
 130 135 140
 Ser Lys Lys Gly Lys Leu His Ala Ser Ala Lys Phe Thr Asp Asp Cys
 145 150 155 160
 Lys Phe Arg Glu Arg Phe Gln Glu Asn Ser Tyr Asn Thr Tyr Ala Ser
 165 170 175
 Ala Ile His Arg Thr Glu Lys Thr Gly Arg Glu Trp Tyr Val Ala Leu
 180 185 190
 Asn Lys Arg Gly Lys Ala Lys Arg Gly Cys Ser Pro Arg Val Lys Pro
 195 200 205
 Gln His Ile Ser Thr His Phe Leu Pro Arg Phe Lys Gln Ser Glu Gln
 210 215 220
 Pro Glu Leu Ser Phe Thr Val Thr Val Pro Glu Lys Lys Asn Pro Pro
 225 230 235 240
 Ser Pro Ile Lys Ser Lys Ile Pro Leu Ser Ala Pro Arg Lys Asn Thr
 245 250 255
 Asn Ser Val Lys Tyr Arg Leu Lys Phe Arg Phe Gly
 260 265

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 Asn Leu Pro Pro Gly Asn Tyr Lys Lys Pro Lys Leu Leu Tyr Cys Ser
 20 25 30
 Asn Gly Gly His Phe Leu Arg Ile Leu Pro Asp Gly Thr Val Asp Gly
 35 40 45
 Thr Arg Asp Arg Ser Asp Gln His Ile Gln Leu Gln Leu Ser Ala Glu
 50 55 60
 Ser Val Gly Glu Val Tyr Ile Lys Ser Thr Glu Thr Gly Gln Tyr Leu
 65 70 75 80
 Ala Met Asp Thr Asp Gly Leu Leu Tyr Gly Ser Gln Thr Pro Asn Glu
 85 90 95
 Glu Cys Leu Phe Leu Glu Arg Leu Glu Glu Asn His Tyr Asn Thr Tyr
 100 105 110
 Ile Ser Lys Lys His Ala Glu Lys Asn Trp Phe Val Gly Leu Lys Lys
 115 120 125
 Asn Gly Ser Cys Lys Arg Gly Pro Arg Thr His Tyr Gly Gln Lys Ala
 130 135 140
 Ile Leu Phe Leu Pro Leu Pro Val Ser Ser Asp
 145 150 155

<210> 17

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<212> PRT

<213> Homo sapiens

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Met Ala Ala Gly Ser Ile Thr Thr Leu Pro Ala Leu Pro Glu Asp Gly
 1 5 10 15
 Gly Ser Gly Ala Phe Pro Pro Gly His Phe Lys Asp Pro Lys Arg Leu
 20 25 30
 Tyr Cys Lys Asn Gly Gly Phe Phe Leu Arg Ile His Pro Asp Gly Arg
 35 40 45
 Val Asp Gly Val Arg Glu Lys Ser Asp Pro His Ile Lys Leu Gln Leu
 50 55 60
 Gln Ala Glu Glu Arg Gly Val Val Ser Ile Lys Gly Val Cys Ala Asn
 65 70 75 80
 Arg Tyr Leu Ala Met Lys Glu Asp Gly Arg Leu Leu Ala Ser Lys Cys
 85 90 95
 Val Thr Asp Glu Cys Phe Phe Phe Glu Arg Leu Glu Ser Asn Asn Tyr
 100 105 110
 Asn Thr Tyr Arg Ser Arg Lys Tyr Thr Ser Trp Tyr Val Ala Leu Lys
 115 120 125

-9-

Arg Thr Gly Gln Tyr Lys Leu Gly Ser Lys Thr Gly Pro Gly Gln Lys
 130 135 140

Ala Ile Leu Phe Leu Pro Met Ser Ala Lys Ser
 145 150 155

<210> 18

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<212> PRT

<213> Homo sapiens

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Met Ala Pro Leu Gly Glu Val Gly Asn Tyr Phe Gly Val Gln Asp Ala
 1 5 10 15

Val Pro Phe Gly Asn Val Pro Val Leu Pro Val Asp Ser Pro Val Leu
 20 25 30

Leu Ser Asp His Leu Gly Gln Ser Glu Ala Gly Gly Leu Pro Arg Gly
 35 40 45

Pro Ala Val Thr Asp Leu Asp His Leu Lys Gly Ile Leu Arg Arg Arg
 50 55 60

Gln Leu Tyr Cys Arg Thr Gly Phe His Leu Glu Ile Phe Pro Asn Gly
 65 70 75 80

Thr Ile Gln Gly Thr Arg Lys Asp His Ser Arg Phe Gly Ile Leu Glu
 85 90 95

Phe Ile Ser Ile Ala Val Gly Leu Val Ser Ile Arg Gly Val Asp Ser
 100 105 110

Gly Leu Tyr Leu Gly Met Asn Glu Lys Gly Glu Leu Tyr Gly Ser Glu
 115 120 125

Lys Leu Thr Gln Glu Cys Val Phe Arg Glu Gln Phe Glu Glu Asn Trp
 130 135 140

Tyr Asn Thr Tyr Ser Ser Asn Leu Tyr Lys His Val Asp Thr Gly Arg
 145 150 155 160

Arg Tyr Tyr Val Ala Leu Asn Lys Asp Gly Thr Pro Arg Glu Gly Thr
 165 170 175

Arg Thr Lys Arg His Gln Lys Phe Thr His Phe Leu Pro Arg Pro Val
 180 185 190

Asp Pro Asp Lys Val Pro Glu Leu Tyr Lys Asp Ile Leu Ser Gln Ser
 195 200 205

<210> 19

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<213> Homo sapiens

<400> 19

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 Ser Cys Phe His Ile Ile Cys Leu Val Gly Thr Ile Ser Leu Ala Cys
 20 25 30
 Asn Asp Met Thr Pro Glu Gln Met Ala Thr Asn Val Asn Cys Ser Ser
 35 40 45
 Pro Glu Arg His Thr Arg Ser Tyr Asp Tyr Met Glu Gly Gly Asp Ile
 50 55 60
 Arg Val Arg Arg Leu Phe Cys Arg Thr Gln Trp Tyr Leu Arg Ile Asp
 65 70 75 80
 Lys Arg Gly Lys Val Lys Gly Thr Gln Glu Met Lys Asn Asn Tyr Asn
 85 90 95
 Ile Met Glu Ile Arg Thr Val Ala Val Gly Ile Val Ala Ile Lys Gly
 100 105 110
 Val Glu Ser Glu Phe Tyr Leu Ala Met Asn Lys Glu Gly Lys Leu Tyr
 115 120 125
 Ala Lys Lys Glu Cys Asn Glu Asp Cys Asn Phe Lys Glu Leu Ile Leu
 130 135 140
 Glu Asn His Tyr Asn Thr Tyr Ala Ser Ala Lys Trp Thr His Asn Gly
 145 150 155 160
 Gly Glu Met Phe Val Ala Leu Asn Gln Lys Gly Ile Pro Val Arg Gly
 165 170 175
 Lys Lys Thr Lys Lys Glu Gln Lys Thr Ala His Phe Leu Pro Met Ala
 180 185 190
 Ile Thr

<210> 20
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 Met Trp Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu
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 Pro Gly Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser
 20 25 30
 Val Pro Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu
 35 40 45
 Ala Thr Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly
 50 55 60
 Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg
 65 70 75 80
 Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly

-11-

85								90				95			
Lys	Val	Ser	Gly 100	Thr	Lys	Lys	Glu	Asn 105	Cys	Pro	Tyr	Ser	Ile 110	Leu	Glu
Ile	Thr	Ser 115	Val	Glu	Ile	Gly	Val 120	Val	Ala	Val	Lys	Ala 125	Ile	Asn	Ser
Asn	Tyr 130	Tyr	Leu	Ala	Met	Asn 135	Lys	Lys	Gly	Lys	Leu 140	Tyr	Gly	Ser	Lys
Glu 145	Phe	Asn	Asn	Asp	Cys 150	Lys	Leu	Lys	Glu	Arg 155	Ile	Glu	Glu	Asn	Gly 160
Tyr	Asn	Thr	Tyr	Ala 165	Ser	Phe	Asn	Trp	Gln 170	His	Asn	Gly	Arg	Gln 175	Met
Tyr	Val	Ala	Leu 180	Asn	Gly	Lys	Gly	Ala 185	Pro	Arg	Arg	Gly	Gln 190	Lys	Thr
Arg	Arg	Lys 195	Asn	Thr	Ser	Ala	His 200	Phe	Leu	Pro	Met	Val 205	Val	His	Ser

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Pro	Ala	Ala	Gly	Pro	Gly	Ala	Arg	Leu	Arg	Arg	Asp	Ala	Gly	Gly	Arg
			20					25					30		
Gly	Gly	Val	Tyr	Glu	His	Leu	Gly	Gly	Ala	Pro	Arg	Arg	Arg	Lys	Leu
		35					40					45			
Tyr	Cys	Ala	Thr	Lys	Tyr	His	Leu	Gln	Leu	His	Pro	Ser	Gly	Arg	Val
	50					55					60				
Asn	Gly	Ser	Leu	Glu	Asn	Ser	Ala	Tyr	Ser	Ile	Leu	Glu	Ile	Thr	Ala
65					70					75					80
Val	Glu	Val	Gly	Ile	Val	Ala	Ile	Arg	Gly	Leu	Phe	Ser	Gly	Arg	Tyr
				85					90					95	
Leu	Ala	Met	Asn	Lys	Arg	Gly	Arg	Leu	Tyr	Ala	Ser	Glu	His	Tyr	Ser
			100					105					110		
Ala	Glu	Cys	Glu	Phe	Val	Glu	Arg	Ile	His	Glu	Leu	Gly	Tyr	Asn	Thr
		115					120					125			
Tyr	Ala	Ser	Arg	Leu	Tyr	Arg	Thr	Val	Ser	Ser	Thr	Pro	Gly	Ala	Arg
	130					135					140				
Arg	Gln	Pro	Ser	Ala	Glu	Arg	Leu	Trp	Tyr	Val	Ser	Val	Asn	Gly	Lys
145					150					155					160

Gly	Arg	Pro	Arg	Arg 165	Gly	Phe	Lys	Thr	Arg 170	Arg	Thr	Gln	Lys	Ser 175	Ser
Leu	Phe	Leu	Pro 180	Arg	Val	Leu	Asp	His 185	Arg	Asp	His	Glu	Met 190	Val	Arg
Gln	Leu	Gln 195	Ser	Gly	Leu	Pro	Arg 200	Pro	Pro	Gly	Lys	Gly 205	Val	Gln	Pro
Arg	Arg 210	Arg	Arg	Gln	Lys	Gln 215	Ser	Pro	Asp	Asn	Leu 220	Glu	Pro	Ser	His
Val 225	Gln	Ala	Ser	Arg	Leu 230	Gly	Ser	Gln	Leu	Glu 235	Ala	Ser	Ala	His	

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<400> 22
Met Gly Ser Pro Arg 5 Ser Ala Leu Ser Cys 10 Leu Leu Leu His Leu 15 Leu
Val Leu Cys 20 Gln Ala Gln Val Arg 25 Ser Ala Ala Gln Lys 30 Arg Gly
Pro Gly Ala 35 Gly Asn Pro Ala Asp 40 Thr Leu Gly Gln Gly 45 His Glu Asp
Arg Pro Phe Gly Gln Arg Ser 55 Arg Ala Gly Lys Asn 60 Phe Thr Asn Pro
Ala 65 Pro Asn Tyr Pro Glu 70 Glu Gly Ser Lys Glu 75 Gln Arg Asp Ser Val 80
Leu Pro Lys Val Thr 85 Gln Arg His Val Arg 90 Glu Gln Ser Leu Val Thr 95
Asp Gln Leu Ser 100 Arg Arg Leu Ile Arg 105 Thr Tyr Gln Leu Tyr 110 Ser Arg
Thr Ser Gly Lys His Val Gln Val 120 Leu Ala Asn Lys Arg 125 Ile Asn Ala
Met Ala Glu Asp Gly Asp Pro 135 Phe Ala Lys Leu Ile 140 Val Glu Thr Asp
Thr Phe Gly Ser Arg Val 150 Arg Val Arg Gly Ala 155 Glu Thr Gly Leu Tyr 160
Ile Cys Met Asn Lys 165 Lys Gly Lys Leu Ile 170 Ala Lys Ser Asn Gly 175 Lys
Gly Lys Asp Cys Val Phe Thr Glu Ile 185 Val Leu Glu Asn Asn 190 Tyr Thr
Ala Leu Gln Asn Ala Lys Tyr Glu 200 Gly Trp Tyr Met Ala 205 Phe Thr Arg
Lys Gly Arg Pro Arg Lys Gly Ser Lys Thr Arg Gln His Gln Arg Glu

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210	215	220
Val His Phe Met Lys Arg Leu Pro Arg Gly His His Thr Thr Glu Gln		
225	230	235 240
Ser Leu Arg Phe Glu Phe Leu Asn Tyr Pro Pro Phe Thr Arg Ser Leu		
	245 250 255	
Arg Gly Ser Gln Arg Thr Trp Ala Pro Glu Pro Arg		
	260 265	

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 ccagaaggtg ccaaccgcag aggggtgcag atatctcccc ctattcccca cccacactcc 180
 cttgggtttt gttcaccgtg ctgtcatctg tttttcagac ctttttggca tctaacatgg 240
 tgaagaaagg agtaaagaag agaacaaagt aactcctggg ggagcgaaga gcgctggtga 300
 ccaacaccac caacgccacc accagctcct gctgctgcgg ccaccacgt ccaccattta 360
 ccgggagggt ccagaggcgt aggcagcgga tccagaaaag gagcgagggg agtcagccgg 420
 cttttccgag gagttatgga tgttggtgca ttcacttctg gccagatccg cgcccagagg 480
 gagctaacca gcagccacca cctcgagctc tctccttgcc ttgcatcggg tcttaccctt 540
 ccagtatgtt ccttctgatg agacaatttc cagtgcgag agtttcagta ca atg tgg 598
 Met Trp
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aaa tgg ata ctg aca cat tgt gcc tca gcc ttt ccc cac ctg ccc ggc 646
 Lys Trp Ile Leu Thr His Cys Ala Ser Ala Phe Pro His Leu Pro Gly
 5 10 15

tgc tgc tgc tgc tgc ttt ttg ttg ctg ttc ttg gtg tct tcc gtc cct 694
 Cys Cys Cys Cys Cys Phe Leu Leu Leu Phe Leu Val Ser Ser Val Pro
 20 25 30

gtc acc tgc caa gcc ctt ggt cag gac atg gtg tca cca gag gcc acc 742
 Val Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
 35 40 45 50

aac tct tct tcc tcc tcc ttc tcc tct cct tcc agc gcg gga agg cat 790
 Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
 55 60 65

gtg cgg agc tac aat cac ctt caa gga gat gtc cgc tgg aga aag cta 838
 Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu

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70	75	80	
ttc tct ttc acc aag tac ttt ctc aag att gag aag aac ggg aag gtc			886
Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val			
85	90	95	
agc ggg acc aag aag gag aac tgc ccg tac agc atc ctg gag ata aca			934
Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr			
100	105	110	
tca gta gaa atc gga gtt gtt gcc gtc aaa gcc att aac agc aac tat			982
Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr			
115	120	125	130
tac tta gcc atg aac aag aag ggg aaa ctc tat ggc tca aaa gaa ttt			1030
Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe			
135	140	145	
aac aat gac tgt aag ctg aag gag agg ata gag gaa aat gga tac aat			1078
Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn			
150	155	160	
acc tat gca tca ttt aac tgg cag cat aat ggg agg caa atg tat gtg			1126
Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val			
165	170	175	
gca ttg aat gga aaa gga gct cca agg aga gga cag aaa aca cga agg			1174
Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg			
180	185	190	
aaa aac acc tct gct cac ttt ctt cca atg gtg gta cac tca			1216
Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser			
195	200	205	
tagaggaagg caacgtttgt ggatgcagta aaaccaatgg ctcttttgcc aagaatagt			1276
gatattcttc atgaagacag tagattgaaa ggcaaagaca cgttgcagat gtctgcttgc			1336
ttaaaagaaa gccagccttt gaaggttttt gtattcactg ctgacatatg atgttctttt			1396
aattagttct gtgtcatgtc ttataatcaa gatataggca gatogaatgg gatagaagtt			1456
attcccaagt gaaaaacatt gtggctgggt tttttgttgt tgttgtcaag tttttgtttt			1516
taaacctctg agatagaact taaaggacat agaacaatct gttgaaagaa cgatcttcgg			1576
gaaagttatt tatggaatac gaactcatat caaagacttc attgctcatt caagccta			1636
gaatcaatga acagtaatac gtgcaagcat ttactggaaa gcacttgggt catatcatat			1696
gcacaaccaa aggagttctg gatgtggtct catggaataa ttgaatagaa tttaaaaata			1756
taaacatggt agtgtgaaac tggttctaaca atacaaatag tatggtatgc ttgtgcattc			1816
tgcttcatc cctttctatt tctttctaag ttattttatt aataggatgt taaatatctt			1876
ttggggtttt aaagagtatc tcagcagctg tcttctgatt tatcttttct ttttattcag			1936
cacaccacat gcatgttcac gacaaagtgt ttttaaaact tggcgaacac ttcaaaaata			1996
ggagttggga ttagggaagc agtatgagtg cccgtgtgct atcagttgac ttaatttgca			2056

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cttctgcagt aataaccatc aacaataaat atggcaatgc tgtgccatgg cttgagtgag 2116
agatgtctgc tatcatttga aaacatatat tactctcgag gcttcctgtc tcaagaaata 2176
gaccagaagg ccaaattctt ctctttcaat acatcagttt gcctccaaga atatactaaa 2236
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ttccacataa tgcattcttc ccaaaggaac tataaagaat ttggtatgaa gcgcaactct 2416
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gtaagacaaa tacacattgg atgaccacag taacagcaaa cagggcacia actggattct 3376
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gccattgcac tccagcctgg gtgaaaaaga gccagaaaga aaggaaagag agaaaagaga 3856
aaagaaagag agaaaagaca gaaagacagg aaggaaggaa ggaaggaagg aaggaaggaa 3916

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ggaagcaagg aaagaaggaa ggaaggaaaag aagggaggga aggaaggaga gagaaagaaa 3976
gattgttttg taaggagtaa tgacattctc ttgcatttaa aagtggcata tttgcttgaa 4036
atggaaatag aattctggtc ccttttgcaa ctactgaaga aaaaaaaaaag cagtttcagc 4096
cctgaatggt gtagatttga aaaaaaaaaa aaaaaaactc gaggggggggc ccgtacccaa 4156
ttcgccctat agtgagtcgt a 4177

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<210> 24
<211> 208
<212> PRT
<213> Homo sapiens
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<400>	24															
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1				5					10					15		
Pro	Gly	Cys	Cys	Cys	Cys	Cys	Phe	Leu	Leu	Leu	Phe	Leu	Val	Ser	Ser	
			20					25					30			
Val	Pro	Val	Thr	Cys	Gln	Ala	Leu	Gly	Gln	Asp	Met	Val	Ser	Pro	Glu	
		35					40					45				
Ala	Thr	Asn	Ser	Ser	Ser	Ser	Ser	Phe	Ser	Ser	Pro	Ser	Ser	Ala	Gly	
	50					55					60					
Arg	His	Val	Arg	Ser	Tyr	Asn	His	Leu	Gln	Gly	Asp	Val	Arg	Trp	Arg	
65					70					75					80	
Lys	Leu	Phe	Ser	Phe	Thr	Lys	Tyr	Phe	Leu	Lys	Ile	Glu	Lys	Asn	Gly	
				85					90					95		
Lys	Val	Ser	Gly	Thr	Lys	Lys	Glu	Asn	Cys	Pro	Tyr	Ser	Ile	Leu	Glu	
			100					105					110			
Ile	Thr	Ser	Val	Glu	Ile	Gly	Val	Val	Ala	Val	Lys	Ala	Ile	Asn	Ser	
		115					120					125				
Asn	Tyr	Tyr	Leu	Ala	Met	Asn	Lys	Lys	Gly	Lys	Leu	Tyr	Gly	Ser	Lys	
	130					135					140					
Glu	Phe	Asn	Asn	Asp	Cys	Lys	Leu	Lys	Glu	Arg	Ile	Glu	Glu	Asn	Gly	
145					150					155					160	
Tyr	Asn	Thr	Tyr	Ala	Ser	Phe	Asn	Trp	Gln	His	Asn	Gly	Arg	Gln	Met	
				165					170					175		
Tyr	Val	Ala	Leu	Asn	Gly	Lys	Gly	Ala	Pro	Arg	Arg	Gly	Gln	Lys	Thr	
			180					185					190			
Arg	Arg	Lys	Asn	Thr	Ser	Ala	His	Phe	Leu	Pro	Met	Val	Val	His	Ser	
		195					200					205				

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<210> 25
<211> 31
<212> PRT
<213> Homo sapiens
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<400> 25

Gly Gln Asp Met Val Ser Pro Glu Ala Thr Asn Ser Ser Ser Ser Ser
 1 5 10 15

Phe Ser Ser Pro Ser Ser Ala Gly Arg His Val Arg Ser Tyr Asn
 20 25 30

<210> 26

<211> 19

<212> PRT

<213> Homo sapiens

<400> 26

Lys Ile Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys
 1 5 10 15

Pro Tyr Ser

<210> 27

<211> 30

<212> PRT

<213> Homo sapiens

<400> 27

Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys
 1 5 10 15

Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr
 20 25 30

<210> 28

<211> 19

<212> PRT

<213> Homo sapiens

<400> 28

Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn
 1 5 10 15

Thr Ser Ala

<210> 29

<211> 555

<212> DNA

<213> Artificial Sequence

<220>

<221> CDS

<222> (1)..(552)

<220>

<223> Description of Artificial Sequence: pQE60-Cys37 construct

<400> 29

atg aga gga tcg cat cac cat cac cat cac gga tcc tgc cag gct ctg 48

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Met	Arg	Gly	Ser	His	His	His	His	His	His	Gly	Ser	Cys	Gln	Ala	Leu	
1				5					10					15		
ggt	cag	gac	atg	gtt	tct	ccg	gaa	gct	acc	aac	tct	tcc	tct	tcc	tct	96
Gly	Gln	Asp	Met	Val	Ser	Pro	Glu	Ala	Thr	Asn	Ser	Ser	Ser	Ser	Ser	
			20					25					30			
ttc	tct	tcc	ccg	tct	tcc	gct	ggg	cgt	cac	gtt	cgt	tct	tac	aac	cac	144
Phe	Ser	Ser	Pro	Ser	Ser	Ala	Gly	Arg	His	Val	Arg	Ser	Tyr	Asn	His	
			35				40					45				
ctg	cag	ggg	gac	gtt	cgt	tgg	cgt	aaa	ctg	ttc	tct	ttc	acc	aaa	tac	192
Leu	Gln	Gly	Asp	Val	Arg	Trp	Arg	Lys	Leu	Phe	Ser	Phe	Thr	Lys	Tyr	
	50					55					60					
ttc	ctg	aaa	atc	gaa	aaa	aac	ggg	aaa	gtt	tct	ggg	acc	aag	aag	gag	240
Phe	Leu	Lys	Ile	Glu	Lys	Asn	Gly	Lys	Val	Ser	Gly	Thr	Lys	Lys	Glu	
65				70					75						80	
aac	tgc	ccg	tac	agc	atc	ctg	gag	ata	aca	tca	gta	gaa	atc	gga	gtt	288
Asn	Cys	Pro	Tyr	Ser	Ile	Leu	Glu	Ile	Thr	Ser	Val	Glu	Ile	Gly	Val	
				85				90						95		
gtt	gcc	gtc	aaa	gcc	att	aac	agc	aac	tat	tac	tta	gcc	atg	aac	aag	336
Val	Ala	Val	Lys	Ala	Ile	Asn	Ser	Asn	Tyr	Tyr	Leu	Ala	Met	Asn	Lys	
			100					105					110			
aag	ggg	aaa	ctc	tat	ggc	tca	aaa	gaa	ttt	aac	aat	gac	tgt	aag	ctg	384
Lys	Gly	Lys	Leu	Tyr	Gly	Ser	Lys	Glu	Phe	Asn	Asn	Asp	Cys	Lys	Leu	
		115					120					125				
aag	gag	agg	ata	gag	gaa	aat	gga	tac	aat	acc	tat	gca	tca	ttt	aac	432
Lys	Glu	Arg	Ile	Glu	Glu	Asn	Gly	Tyr	Asn	Thr	Tyr	Ala	Ser	Phe	Asn	
	130					135					140					
tgg	cag	cat	aat	ggg	agg	caa	atg	tat	gtg	gca	ttg	aat	gga	aaa	gga	480
Trp	Gln	His	Asn	Gly	Arg	Gln	Met	Tyr	Val	Ala	Leu	Asn	Gly	Lys	Gly	
145				150					155					160		
gct	cca	agg	aga	gga	cag	aaa	aca	cga	agg	aaa	aac	acc	tct	gct	cac	528
Ala	Pro	Arg	Arg	Gly	Gln	Lys	Thr	Arg	Arg	Lys	Asn	Thr	Ser	Ala	His	
				165				170						175		
ttt	ctt	cca	atg	gtg	gta	cac	tca	tag								555
Phe	Leu	Pro	Met	Val	Val	His	Ser									
			180													

<210> 30

<211> 184

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence: pQE60-Cys37 construct

<400> 30

Met	Arg	Gly	Ser	His	His	His	His	His	His	Gly	Ser	Cys	Gln	Ala	Leu
1				5					10					15	

Gly	Gln	Asp	Met	Val	Ser	Pro	Glu	Ala	Thr	Asn	Ser	Ser	Ser	Ser	Ser
			20					25					30		

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Phe Ser Ser Pro Ser Ser Ala Gly Arg His Val Arg Ser Tyr Asn His
 35 40 45
 Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr
 50 55 60
 Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu
 65 70 75 80
 Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val
 85 90 95
 Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys
 100 105 110
 Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu
 115 120 125
 Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn
 130 135 140
 Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly
 145 150 155 160
 Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His
 165 170 175
 Phe Leu Pro Met Val Val His Ser
 180

<210> 31
 <211> 84
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: synthetic
 primer

<400> 31
 atgtggaaat ggatactgac ccaactgcgt tctgctttcc cgcacctgcc gggttgctgc 60
 tgctgctgct tctgctgct gttc 84

<210> 32
 <211> 82
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: synthetic
 primer

<400> 32
 ccggagaaac catgtcctga cccagagcct ggcaggtaac cggaacagaa gaaaccagga 60
 acagcagcag gaagcagcag ca 82

<210> 33
 <211> 80

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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
primer

<400> 33
gggtcaggac atggtttctc cggaagctac caactcttct tcttcttctt tctcttctcc 60
gtcttctgct ggtcgtcacg 80

<210> 34
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
primer

<400> 34
ggtgaaagag aacagtttac gccaacgaac gtcaccctgc aggtggttgt aagaacgaac 60
gtgacgacca gcagaagacg g 81

<210> 35
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
primer

<400> 35
cgttggcgta aactgttctc tttcaccaaa tacttcctga aaatcgaaaa aaacggtaaa 60
gtttctggga ccaaa 75

<210> 36
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
primer

<400> 36
tttgggtccca gaaactttac cgtttttttc gattttcag 39

<210> 37
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
primer

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<400> 37

aaaggatcca tgtggaaatg gatactgacc cactgc

36

<210> 38

<211> 627

<212> DNA

<213> Escherichia coli

<220>

<221> CDS

<222> (1)..(627)

<400> 38

atg	tgg	aaa	tgg	ata	ctg	acc	cac	tgc	gct	tct	gct	ttc	ccg	cac	ctg	48
Met	Trp	Lys	Trp	Ile	Leu	Thr	His	Cys	Ala	Ser	Ala	Phe	Pro	His	Leu	
1				5				10				15				
ccg	ggt	tgc	tgc	tgc	tgc	tgc	ttc	ctg	ctg	ctg	ttc	ctg	ggt	tct	tct	96
Pro	Gly	Cys	Cys	Cys	Cys	Cys	Phe	Leu	Leu	Leu	Phe	Leu	Val	Ser	Ser	
			20					25					30			
ggt	ccg	ggt	acc	tgc	cag	gct	ctg	ggt	cag	gac	atg	ggt	tct	ccg	gaa	144
Val	Pro	Val	Thr	Cys	Gln	Ala	Leu	Gly	Gln	Asp	Met	Val	Ser	Pro	Glu	
			35				40					45				
gct	acc	aac	tct	tcc	tct	tcc	tct	ttc	tct	tcc	ccg	act	tcc	gct	ggt	192
Ala	Thr	Asn	Ser	Ser	Ser	Ser	Ser	Phe	Ser	Ser	Pro	Thr	Ser	Ala	Gly	
	50					55					60					
cgt	cac	ggt	cgt	tct	tac	aac	cac	ctg	cag	ggt	gac	ggt	cgt	tgg	cgt	240
Arg	His	Val	Arg	Ser	Tyr	Asn	His	Leu	Gln	Gly	Asp	Val	Arg	Trp	Arg	
	65				70				75					80		
aaa	ctg	ttc	tct	ttc	acc	aaa	tac	ttc	ctg	aaa	atc	gaa	aaa	aac	ggt	288
Lys	Leu	Phe	Ser	Phe	Thr	Lys	Tyr	Phe	Leu	Lys	Ile	Glu	Lys	Asn	Gly	
				85					90					95		
aaa	ggt	tct	ggg	acc	aag	aag	gag	aac	tgc	ccg	tac	agc	atc	ctg	gag	336
Lys	Val	Ser	Gly	Thr	Lys	Lys	Glu	Asn	Cys	Pro	Tyr	Ser	Ile	Leu	Glu	
			100				105						110			
ata	aca	tca	gta	gaa	atc	gga	ggt	ggt	gcc	gtc	aaa	gcc	att	aac	agc	384
Ile	Thr	Ser	Val	Glu	Ile	Gly	Val	Val	Ala	Val	Lys	Ala	Ile	Asn	Ser	
			115				120					125				
aac	tat	tac	tta	gcc	atg	aac	aag	aag	ggg	aaa	ctc	tat	ggc	tca	aaa	432
Asn	Tyr	Tyr	Leu	Ala	Met	Asn	Lys	Lys	Gly	Lys	Leu	Tyr	Gly	Ser	Lys	
	130					135					140					
gaa	ttt	aac	aat	gac	tgt	aag	ctg	aag	gag	agg	ata	gag	gaa	aat	gga	480
Glu	Phe	Asn	Asn	Asp	Cys	Lys	Leu	Lys	Glu	Arg	Ile	Glu	Glu	Asn	Gly	
	145				150				155					160		
tac	aat	acc	tat	gca	tca	ttt	aac	tgg	cag	cat	aat	ggg	agg	caa	atg	528
Tyr	Asn	Thr	Tyr	Ala	Ser	Phe	Asn	Trp	Gln	His	Asn	Gly	Arg	Gln	Met	
				165					170					175		
tat	gtg	gca	ttg	aat	gga	aaa	gga	gct	cca	agg	aga	gga	cag	aaa	aca	576
Tyr	Val	Ala	Leu	Asn	Gly	Lys	Gly	Ala	Pro	Arg	Arg	Gly	Gln	Lys	Thr	
			180					185					190			

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cga agg aaa aac acc tct gct cac ttt ctt cca atg gtg gta cac tca 624
Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
195 200 205

tag 627

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<210> 39
<211> 208
<212> PRT
<213> Escherichia coli
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<400>	39															
Met	Trp	Lys	Trp	Ile	Leu	Thr	His	Cys	Ala	Ser	Ala	Phe	Pro	His	Leu	
1				5					10					15		
Pro	Gly	Cys	Cys	Cys	Cys	Cys	Phe	Leu	Leu	Leu	Phe	Leu	Val	Ser	Ser	
			20					25					30			
Val	Pro	Val	Thr	Cys	Gln	Ala	Leu	Gly	Gln	Asp	Met	Val	Ser	Pro	Glu	
		35					40					45				
Ala	Thr	Asn	Ser	Ser	Ser	Ser	Ser	Phe	Ser	Ser	Pro	Thr	Ser	Ala	Gly	
	50					55					60					
Arg	His	Val	Arg	Ser	Tyr	Asn	His	Leu	Gln	Gly	Asp	Val	Arg	Trp	Arg	
65					70					75					80	
Lys	Leu	Phe	Ser	Phe	Thr	Lys	Tyr	Phe	Leu	Lys	Ile	Glu	Lys	Asn	Gly	
				85					90					95		
Lys	Val	Ser	Gly	Thr	Lys	Lys	Glu	Asn	Cys	Pro	Tyr	Ser	Ile	Leu	Glu	
			100					105					110			
Ile	Thr	Ser	Val	Glu	Ile	Gly	Val	Val	Ala	Val	Lys	Ala	Ile	Asn	Ser	
			115				120					125				
Asn	Tyr	Tyr	Leu	Ala	Met	Asn	Lys	Lys	Gly	Lys	Leu	Tyr	Gly	Ser	Lys	
	130					135					140					
Glu	Phe	Asn	Asn	Asp	Cys	Lys	Leu	Lys	Glu	Arg	Ile	Glu	Glu	Asn	Gly	
145					150					155					160	
Tyr	Asn	Thr	Tyr	Ala	Ser	Phe	Asn	Trp	Gln	His	Asn	Gly	Arg	Gln	Met	
				165					170					175		
Tyr	Val	Ala	Leu	Asn	Gly	Lys	Gly	Ala	Pro	Arg	Arg	Gly	Gln	Lys	Thr	
			180					185					190			
Arg	Arg	Lys	Asn	Thr	Ser	Ala	His	Phe	Leu	Pro	Met	Val	Val	His	Ser	
		195					200					205				

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<210> 40
<211> 38
<212> DNA
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: primer

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<400> 40
tttcatgact tgtcaagctc tgggtcaaga tatggttc 38
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<210> 41
<211> 28
<212> DNA
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: primer

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<400> 41
gccccaaagctt ccacaaacgt tgccttcc

28

<210> 42
<211> 525
<212> DNA
<213> Escherichia coli

<220>
<221> CDS
<222> (1)..(522)

<400> 42
atg acc tgc cag gct ctg ggt cag gac atg gtt tct ccg gaa gct acc 48
Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
1 5 10 15
aac tct tcc tct tcc tct ttc tct tcc ccg tct tcc gct ggt cgt cac 96
Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
20 25 30
gtt cgt tct tac aac cac ctg cag ggt gac gtt cgt tgg cgt aaa ctg 144
Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
35 40 45
ttc tct ttc acc aaa tac ttc ctg aaa atc gaa aaa aac ggt aaa gtt 192
Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
50 55 60
tct ggg acc aag aag gag aac tgc ccg tac agc atc ctg gag ata aca 240
Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
65 70 75 80
tca gta gaa atc gga gtt gtt gcc gtc aaa gcc att aac agc aac tat 288
Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
85 90 95
tac tta gcc atg aac aag aag ggg aaa ctc tat ggc tca aaa gaa ttt 336
Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
100 105 110
aac aat gac tgt aag ctg aag gag agg ata gag gaa aat gga tac aat 384
Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn
115 120 125
acc tat gca tca ttt aac tgg cag cat aat ggg agg caa atg tat gtg 432
Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val
130 135 140
gca ttg aat gga aaa gga gct cca agg aga gga cag aaa aca cga agg 480
Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg
145 150 155 160
aaa aac acc tct gct cac ttt ctt cca atg gtg gta cac tca tag 525
Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
165 170

<210> 43
<211> 174
<212> PRT

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<213> Escherichia coli

<400> 43

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Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
 1           5           10           15
Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
          20           25           30
Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
          35           40           45
Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
          50           55           60
Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
          65           70           75           80
Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
          85           90           95
Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
          100          105          110
Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn
          115          120          125
Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val
          130          135          140
Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg
          145          150          155          160
Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
          165          170

```

<210> 44

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic primer

<400> 44

tcagtgaatt cattaaagag gagaaattaa tcatgacttg ccagg

45

<210> 45

<211> 48

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic primer

<400> 45

tcatgacttg ccaggcactg ggtcaagaca tggtttcccc ggaagcta

48

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<210> 46
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 46
gcttcagcag cccatctagc gcaggtcgtc acgttcgctc ttacaacc 48

<210> 47
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 47
gttcgttggc gcaaactggt cagctttacc aagtacttcc tgaaaatc 48

<210> 48
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 48
tcgaaaaaaa cggtaaagtt tctgggac 28

<210> 49
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

<400> 49
gatgggctgc tgaagctaga gctggagctg ttggtagctt ccggggaa 48

<210> 50
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic primer

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<400> 50
 aacagtttgc gccaacgaac atcacctgt aagtggttgt aagag 45

<210> 51
 <211> 47
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: synthetic primer

<400> 51
 ttcttgggtcc cagaaacttt accgtttttt tcgattttca ggaagta 47

<210> 52
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: synthetic primer

<400> 52
 ttcttgggtcc cagaaacttt accg 24

<210> 53
 <211> 45
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: synthetic primer

<400> 53
 agatcaggct tctattatta tgagtgtacc accattggaa gaaag 45

<210> 54
 <211> 525
 <212> DNA
 <213> Escherichia coli

<220>
 <221> CDS
 <222> (1)..(522)

<400> 54
 atg act tgc cag gca ctg ggt caa gac atg gtt tcc ccg gaa gct acc 48
 Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
 1 5 10 15

aac agc tcc agc tct agc ttc agc agc cca tct agc gca ggt cgt cac 96
 Asn Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
 20 25 30

gtt cgc tct tac aac cac tta cag ggt gat gtt cgt tgg cgc aaa ctg 144

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Val	Arg	Ser	Tyr	Asn	His	Leu	Gln	Gly	Asp	Val	Arg	Trp	Arg	Lys	Leu		
		35					40					45					
ttc	agc	ttt	acc	aag	tac	ttc	ctg	aaa	atc	gaa	aaa	aac	ggg	aaa	gtt	192	
Phe	Ser	Phe	Thr	Lys	Tyr	Phe	Leu	Lys	Ile	Glu	Lys	Asn	Gly	Lys	Val		
	50					55					60						
tct	ggg	acc	aag	aag	gag	aac	tgc	ccg	tac	agc	atc	ctg	gag	ata	aca	240	
Ser	Gly	Thr	Lys	Lys	Glu	Asn	Cys	Pro	Tyr	Ser	Ile	Leu	Glu	Ile	Thr		
	65				70				75						80		
tca	gta	gaa	atc	gga	gtt	gtt	gcc	gtc	aaa	gcc	att	aac	agc	aac	tat	288	
Ser	Val	Glu	Ile	Gly	Val	Val	Ala	Val	Lys	Ala	Ile	Asn	Ser	Asn	Tyr		
				85					90					95			
tac	tta	gcc	atg	aac	aag	aag	ggg	aaa	ctc	tat	ggc	tca	aaa	gaa	ttt	336	
Tyr	Leu	Ala	Met	Asn	Lys	Lys	Gly	Lys	Leu	Tyr	Gly	Ser	Lys	Glu	Phe		
			100					105					110				
aac	aat	gac	tgt	aag	ctg	aag	gag	agg	ata	gag	gaa	aat	gga	tac	aat	384	
Asn	Asn	Asp	Cys	Lys	Leu	Lys	Glu	Arg	Ile	Glu	Glu	Asn	Gly	Tyr	Asn		
		115					120					125					
acc	tat	gca	tca	ttt	aac	tgg	cag	cat	aat	ggg	agg	caa	atg	tat	gtg	432	
Thr	Tyr	Ala	Ser	Phe	Asn	Trp	Gln	His	Asn	Gly	Arg	Gln	Met	Tyr	Val		
		130				135					140						
gca	ttg	aat	gga	aaa	gga	gct	cca	agg	aga	gga	cag	aaa	aca	cga	agg	480	
Ala	Leu	Asn	Gly	Lys	Gly	Ala	Pro	Arg	Arg	Gly	Gln	Lys	Thr	Arg	Arg		
	145				150					155					160		
aaa	aac	acc	tct	gct	cac	ttt	ctt	cca	atg	gtg	gta	cac	tca	tag		525	
Lys	Asn	Thr	Ser	Ala	His	Phe	Leu	Pro	Met	Val	Val	His	Ser				
				165					170								

<210> 55

<211> 174

<212> PRT

<213> Escherichia coli

<400> 55

Met	Thr	Cys	Gln	Ala	Leu	Gly	Gln	Asp	Met	Val	Ser	Pro	Glu	Ala	Thr
1				5					10					15	

Asn	Ser	Ser	Ser	Ser	Ser	Phe	Ser	Ser	Pro	Ser	Ser	Ala	Gly	Arg	His
			20					25					30		

Val	Arg	Ser	Tyr	Asn	His	Leu	Gln	Gly	Asp	Val	Arg	Trp	Arg	Lys	Leu
		35					40					45			

Phe	Ser	Phe	Thr	Lys	Tyr	Phe	Leu	Lys	Ile	Glu	Lys	Asn	Gly	Lys	Val
	50					55					60				

Ser	Gly	Thr	Lys	Lys	Glu	Asn	Cys	Pro	Tyr	Ser	Ile	Leu	Glu	Ile	Thr
	65				70				75						80

Ser	Val	Glu	Ile	Gly	Val	Val	Ala	Val	Lys	Ala	Ile	Asn	Ser	Asn	Tyr
				85					90					95	

Tyr	Leu	Ala	Met	Asn	Lys	Lys	Gly	Lys	Leu	Tyr	Gly	Ser	Lys	Glu	Phe
			100					105						110	

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Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn
 115 120 125

Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val
 130 135 140

Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg
 145 150 155 160

Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
 165 170

<210> 56
 <211> 35
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

<400> 56
 ggaccctcat gacctgccag gctctgggtc aggac 35

<210> 57
 <211> 28
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

<400> 57
 ggacagccat ggctggtcgt cacgttcg 28

<210> 58
 <211> 29
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

<400> 58
 ggacagccat gggtcgttgg cgtaaactg 29

<210> 59
 <211> 31
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

<400> 59
 ggacagccat ggaaaaaac ggtaaagttt c 31

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<210> 60
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 60
ggacccccat ggagaactgc ccgtagagc 29

<210> 61
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 61
ggacccccat ggtcaaagcc attaacagca ac 32

<210> 62
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 62
ggacccccat ggggaaactc tatggctcaa aag 33

<210> 63
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 63
ctgccaagc ttattatgag tgtaccacca ttggaag 37

<210> 64
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 64
ctgccaagc ttattacttc agcttacagt cattgt 36

<210> 65
<211> 525

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<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(522)

<400> 65

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atg acc tgc cag gct ctg ggt cag gac atg gtt tct ccg gaa gct acc 48
Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
  1           5           10           15

aac tct tcc tct tcc tct ttc tct tcc ccg tct tcc gct ggt cgt cac 96
Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
           20           25           30

gtt cgt tct tac aac cac ctg cag ggt gac gtt cgt tgg cgt aaa ctg 144
Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
           35           40           45

ttc tct ttc acc aaa tac ttc ctg aaa atc gaa aaa aac ggt aaa gtt 192
Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
           50           55           60

tct ggg acc aag aag gag aac tgc ccg tac agc atc ctg gag ata aca 240
Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
           65           70           75           80

tca gta gaa atc gga gtt gtt gcc gtc aaa gcc att aac agc aac tat 288
Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
           85           90           95

tac tta gcc atg aac aag aag ggg aaa ctc tat ggc tca aaa gaa ttt 336
Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
           100          105          110

aac aat gac tgt aag ctg aag gag agg ata gag gaa aat gga tac aat 384
Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn
           115          120          125

acc tat gca tca ttt aac tgg cag cat aat ggg agg caa atg tat gtg 432
Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val
           130          135          140

gca ttg aat gga aaa gga gct cca agg aga gga cag aaa aca cga agg 480
Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg
           145          150          155          160

aaa aac acc tct gct cac ttt ctt cca atg gtg gta cac tca tag 525
Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
           165          170

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<210> 66

<211> 174

<212> PRT

<213> Homo sapiens

<400> 66

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Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
  1           5           10           15

```

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Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
 20 25 30
 Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
 35 40 45
 Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
 50 55 60
 Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
 65 70 75 80
 Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
 85 90 95
 Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
 100 105 110
 Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn
 115 120 125
 Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val
 130 135 140
 Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg
 145 150 155 160
 Lys Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
 165 170

<210> 67

<211> 444

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(444)

<400> 67

atg gct ggt cgt cac gtt cgt tct tac aac cac ctg cag ggt gac gtt 48
 Met Ala Gly Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val
 1 5 10 15
 cgt tgg cgt aaa ctg ttc tct ttc acc aaa tac ttc ctg aaa atc gaa 96
 Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu
 20 25 30
 aaa aac ggt aaa gtt tct ggg acc aag gag aac tgc ccg tac agc 144
 Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser
 35 40 45
 atc ctg gag ata aca tca gta gaa atc gga gtt gtt gcc gtc aaa gcc 192
 Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala
 50 55 60
 att aac agc aac tat tac tta gcc atg aac aag aag ggg aaa ctc tat 240
 Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr
 65 70 75 80

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```

ggc tca aaa gaa ttt aac aat gac tgt aag ctg aag gag agg ata gag 288
Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu
                        85                      90                      95

gaa aat gga tac aat acc tat gca tca ttt aac tgg cag cat aat ggg 336
Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly
                        100                      105                      110

agg caa atg tat gtg gca ttg aat gga aaa gga gct cca agg aga gga 384
Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly
                        115                      120                      125

cag aaa aca cga agg aaa aac acc tct gct cac ttt ctt cca atg gtg 432
Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val
                        130                      135                      140

gta cac tca tag 444
Val His Ser
145

```

<210> 68
 <211> 147
 <212> PRT
 <213> Homo sapiens

```

<400> 68
Met Ala Gly Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val
1      5      10      15
Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu
      20      25      30
Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser
      35      40      45
Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala
      50      55      60
Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr
      65      70      75      80
Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu
      85      90      95
Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His Asn Gly
      100      105      110
Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly
      115      120      125
Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro Met Val
      130      135      140
Val His Ser
145

```

<210> 69
 <211> 402
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(402)

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<400> 69
atg gtt cgt tgg cgt aaa ctg ttc tct ttc acc aaa tac ttc ctg aaa 48
Met Val Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys

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1	5	10	15	
atc gaa aaa aac ggt aaa gtt tct ggg acc aag aag gag aac tgc ccg	Ile Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro	96		
	20	25	30	
tac agc atc ctg gag ata aca tca gta gaa atc gga gtt gtt gcc gtc	Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val	144		
	35	40	45	
aaa gcc att aac agc aac tat tac tta gcc atg aac aag aag ggg aaa	Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys	192		
	50	55	60	
ctc tat ggc tca aaa gaa ttt aac aat gac tgt aag ctg aag gag agg	Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg	240		
	65	70	75	80
ata gag gaa aat gga tac aat acc tat gca tca ttt aac tgg cag cat	Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His	288		
	85	90	95	
aat ggg agg caa atg tat gtg gca ttg aat gga aaa gga gct cca agg	Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg	336		
	100	105	110	
aga gga cag aaa aca cga agg aaa aac acc tct gct cac ttt ctt cca	Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro	384		
	115	120	125	
atg gtg gta cac tca tag	Met Val Val His Ser	402		
	130			

<210> 70

<211> 133

<212> PRT

<213> Homo sapiens

<400> 70

Met Val Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys	1	5	10	15
Ile Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro	20	25	30	
Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val	35	40	45	
Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys	50	55	60	
Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg	65	70	75	80
Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His	85	90	95	
Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg	100	105	110	
Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro	115	120	125	
Met Val Val His Ser	130			

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<210> 71
 <211> 354
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(354)

<400> 71
 atg gaa aaa aac ggt aaa gtt tct ggg acc aag aag gag aac tgc ccg 48
 Met Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro
 1 5 10 15
 tac agc atc ctg gag ata aca tca gta gaa atc gga gtt gtt gcc gtc 96
 Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val
 20 25 30
 aaa gcc att aac agc aac tat tac tta gcc atg aac aag aag ggg aaa 144
 Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys
 35 40 45
 ctc tat ggc tca aaa gaa ttt aac aat gac tgt aag ctg aag gag agg 192
 Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg
 50 55 60
 ata gag gaa aat gga tac aat acc tat gca tca ttt aac tgg cag cat 240
 Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His
 65 70 75 80
 aat ggg agg caa atg tat gtg gca ttg aat gga aaa gga gct cca agg 288
 Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg
 85 90 95
 aga gga cag aaa aca cga agg aaa aac acc tct gct cac ttt ctt cca 336
 Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro
 100 105 110
 atg gtg gta cac tca tag 354
 Met Val Val His Ser
 115

<210> 72
 <211> 117
 <212> PRT
 <213> Homo sapiens

<400> 72
 Met Glu Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro
 1 5 10 15
 Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val
 20 25 30
 Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys
 35 40 45
 Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys Glu Arg
 50 55 60
 Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp Gln His
 65 70 75 80
 Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala Pro Arg
 85 90 95
 Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe Leu Pro

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100
Met Val Val His Ser
115

105

110

<210> 73
<211> 321
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(321)

<400> 73
atg gag aac tgc ccg tac agc atc ctg gag ata aca tca gta gaa atc 48
Met Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile
1 5 10 15
gga gtt gtt gcc gtc aaa gcc att aac agc aac tat tac tta gcc atg 96
Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met
20 25 30
aac aag aag ggg aaa ctc tat ggc tca aaa gaa ttt aac aat gac tgt 144
Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys
35 40 45
aag ctg aag gag agg ata gag gaa aat gga tac aat acc tat gca tca 192
Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser
50 55 60
ttt aac tgg cag cat aat ggg agg caa atg tat gtg gca ttg aat gga 240
Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly
65 70 75 80
aaa gga gct cca agg aga gga cag aaa aca cga agg aaa aac acc tct 288
Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser
85 90 95
gct cac ttt ctt cca atg gtg gta cac tca tag 321
Ala His Phe Leu Pro Met Val Val His Ser
100 105

<210> 74
<211> 106
<212> PRT
<213> Homo sapiens

<400> 74
Met Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser Val Glu Ile
1 5 10 15
Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met
20 25 30
Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys
35 40 45
Lys Leu Lys Glu Arg Ile Glu Asn Gly Tyr Asn Thr Tyr Ala Ser
50 55 60
Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly
65 70 75 80
Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser

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85 90 95
 Ala His Phe Leu Pro Met Val Val His Ser
 100 105

<210> 75
 <211> 264
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(261)

<400> 75
 atg gtc aaa gcc att aac agc aac tat tac tta gcc atg aac aag aag 48
 Met Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys
 1 5 10 15
 ggg aaa ctc tat ggc tca aaa gaa ttt aac aat gac tgt aag ctg aag 96
 Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys
 20 25 30
 gag agg ata gag gaa aat gga tac aat acc tat gca tca ttt aac tgg 144
 Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp
 35 40 45
 cag cat aat ggg agg caa atg tat gtg gca ttg aat gga aaa gga gct 192
 Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala
 50 55 60
 cca agg aga gga cag aaa aca cga agg aaa aac acc tct gct cac ttt 240
 Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe
 65 70 75 80
 ctt cca atg gtg gta cac tca tag 264
 Leu Pro Met Val Val His Ser
 85

<210> 76
 <211> 87
 <212> PRT
 <213> Homo sapiens

<400> 76
 Met Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys
 1 5 10 15
 Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys
 20 25 30
 Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn Trp
 35 40 45
 Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly Ala
 50 55 60
 Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His Phe
 65 70 75 80

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Leu Pro Met Val Val His Ser
85

<210> 77
<211> 219
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(219)

<400> 77
atg ggg aaa ctc tat ggc tca aaa gaa ttt aac aat gac tgt aag ctg 48
Met Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu
1 5 10 15
aag gag agg ata gag gaa aat gga tac aat acc tat gca tca ttt aac 96
Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn
20 25 30
tgg cag cat aat ggg agg caa atg tat gtg gca ttg aat gga aaa gga 144
Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly
35 40 45
gct cca agg aga gga cag aaa aca cga agg aaa aac acc tct gct cac 192
Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His
50 55 60
ttt ctt cca atg gtg gta cac tca tag 219
Phe Leu Pro Met Val Val His Ser
65 70

<210> 78
<211> 72
<212> PRT
<213> Homo sapiens

<400> 78
Met Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu
1 5 10 15
Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr Ala Ser Phe Asn
20 25 30
Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu Asn Gly Lys Gly
35 40 45
Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys Asn Thr Ser Ala His
50 55 60
Phe Leu Pro Met Val Val His Ser
65 70

<210> 79
<211> 357
<212> DNA
<213> Homo sapiens

<220>
<221> CDS

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<222> (1)..(357)

<400> 79

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atg acc tgc cag gct ctg ggt cag gac atg gtt tct ccg gaa gct acc 48
Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
  1             5             10             15

aac tct tcc tct tcc tct ttc tct tcc ccg tct tcc gct ggt cgt cac 96
Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
             20             25             30

gtt cgt tct tac aac cac ctg cag ggt gac gtt cgt tgg cgt aaa ctg 144
Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
             35             40             45

ttc tct ttc acc aaa tac ttc ctg aaa atc gaa aaa aac ggt aaa gtt 192
Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
             50             55             60

tct ggg acc aag aag gag aac tgc ccg tac agc atc ctg gag ata aca 240
Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
             65             70             75             80

tca gta gaa atc gga gtt gtt gcc gtc aaa gcc att aac agc aac tat 288
Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
             85             90             95

tac tta gcc atg aac aag aag ggg aaa ctc tat ggc tca aaa gaa ttt 336
Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
             100             105             110

aac aat gac tgt aag ctg aag 357
Asn Asn Asp Cys Lys Leu Lys
             115

```

<210> 80

<211> 119

<212> PRT

<213> Homo sapiens

<400> 80

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Met Thr Cys Gln Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr
  1             5             10             15

Asn Ser Ser Ser Ser Ser Phe Ser Ser Pro Ser Ser Ala Gly Arg His
             20             25             30

Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu
             35             40             45

Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val
             50             55             60

Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr
             65             70             75             80

Ser Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr
             85             90             95

Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe
             100             105             110

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Asn Asn Asp Cys Lys Leu Lys
115

<210> 81
<211> 276
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(276)

<400> 81
atg gct ggt cgt cac gtt cgt tct tac aac cac ctg cag ggt gac gtt 48
Met Ala Gly Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val
1 5 10 15
cgt tgg cgt aaa ctg ttc tct ttc acc aaa tac ttc ctg aaa atc gaa 96
Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu
20 25 30
aaa aac ggt aaa gtt tct ggg acc aag aag gag aac tgc ccg tac agc 144
Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser
35 40 45
atc ctg gag ata aca tca gta gaa atc gga gtt gtt gcc gtc aaa gcc 192
Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala
50 55 60
att aac agc aac tat tac tta gcc atg aac aag aag ggg aaa ctc tat 240
Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr
65 70 75 80
ggc tca aaa gaa ttt aac aat gac tgt aag ctg aag 276
Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys
85 90

<210> 82
<211> 92
<212> PRT
<213> Homo sapiens

<400> 82
Met Ala Gly Arg His Val Arg Ser Tyr Asn His Leu Gln Gly Asp Val
1 5 10 15
Arg Trp Arg Lys Leu Phe Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu
20 25 30
Lys Asn Gly Lys Val Ser Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser
35 40 45
Ile Leu Glu Ile Thr Ser Val Glu Ile Gly Val Val Ala Val Lys Ala
50 55 60
Ile Asn Ser Asn Tyr Tyr Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr
65 70 75 80
Gly Ser Lys Glu Phe Asn Asn Asp Cys Lys Leu Lys

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85

90

<210> 83
 <211> 525
 <212> DNA
 <213> Homo sapiens

<400> 83
 atgacctctc aggcctctggg tcaggacatg gtttctccgg aagctaccaa ctcttcctct 60
 tcctctttct cttccccgtc ttccgctggg cgtcacgttc gttcttacia ccacctgcag 120
 ggtgacgttc gttggcgtaa actgttctct ttcaccaaact acttcttgaa aatcgaaaaa 180
 aacggtaaaag tttctgggac caagaaggag aactctccgt acagcatcct ggagataaca 240
 tcagtagaaa tcggagttgt tgccgtcaaa gccattaaca gcaactatta cttagccatg 300
 aacaagaagg ggaaactcta tggctcaaaa gaatttaaca atgactgtaa gctgaaggag 360
 aggatagagg aaaatggata caatacctat gcatcattta actggcagca taatgggagg 420
 caaatgtatg tggcattgaa tggaaaagga gctccaagga gaggacagaa aacacgaagg 480
 aaaaacacct ctgctcactt tcttccaatg gtggtacact catag 525

<210> 84
 <211> 525
 <212> DNA
 <213> Homo sapiens

<400> 84
 atgacctgcc aggcctctggg tcaggacatg gtttctccgg aagctaccaa ctcttcctct 60
 tcctctttct cttccccgtc ttccgctggg cgtcacgttc gttcttacia ccacctgcag 120
 ggtgacgttc gttggcgtaa actgttctct ttcaccaaact acttcttgaa aatcgaaaaa 180
 aacggtaaaag tttctgggac caagaaggag aactctccgt acagcatcct ggagataaca 240
 tcagtagaaa tcggagttgt tgccgtcaaa gccattaaca gcaactatta cttagccatg 300
 aacaagaagg ggaaactcta tggctcaaaa gaatttaaca atgactgtaa gctgaaggag 360
 aggatagagg aaaatggata caatacctat gcatcattta actggcagca taatgggagg 420
 caaatgtatg tggcattgaa tggaaaagga gctccaagga gaggacagaa aacacgaagg 480
 aaaaacacct ctgctcactt tcttccaatg gtggtacact catag 525

<210> 85
 <211> 29
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

<400> 85
 ggaccctcat gacctctcag gctctgggt 29

<210> 86
 <211> 21
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

<400> 86
 aaggagaact ctccgtacag c 21

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<210> 87
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 87
gctgtacggg ctgttctcct t 21

<210> 88
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 88
ggaccctcat gacctgccag gctctgggtc aggac 35

<210> 89
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 89
ctgcccaagc ttattatgag tgtaccacca ttggaag 37

<210> 90
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 90
aaaggatcct gccaggctct gggtcaggac atg 33

<210> 91
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 91
gcggcacatg tcttacaacc acctgcaggg tg 32

<210> 92
<211> 28

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<212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

<400> 92
 gggccccaagc ttatgagtgt accaccat 28

<210> 93
 <211> 36
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

<400> 93
 ccggcggtac ccatatgtct tacaaccacc tgcagg 36

<210> 94
 <211> 35
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

<400> 94
 ccggcggtac cttattatga gtgtaccacc attgg 35

<210> 95
 <211> 426
 <212> DNA
 <213> Homo sapiens

<400> 95
 atgtcttaca accacctgca gggtgacgtt cgttggcgta aactgttctc tttcaccaaa 60
 tacttctctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcceg 120
 tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
 agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
 aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcatcattt 300
 aactggcagc ataatgggag gcaaattgtat gtggcattga atggaaaagg agctccaagg 360
 agaggacaga aaacacgaag gaaaaacacc tctgtctact ttcttccaat ggtggtacac 420
 tcataa 426

<210> 96
 <211> 141
 <212> PRT
 <213> Homo sapiens

<400> 96
 Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
 1 5 10 15
 Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
 20 25 30

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Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
 35 40 45
 Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
 50 55 60
 Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
 65 70 75 80
 Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
 85 90 95
 Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
 100 105 110
 Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys
 115 120 125
 Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
 130 135 140

<210> 97
 <211> 20
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:
 oligonucleotide

<400> 97
 caaccacctg caggggtgacg

20

<210> 98
 <211> 78
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:
 oligonucleotide

<400> 98
 aacggtcgac aaatgtatgt ggcaactgaac ggtaaagggtg ctccacgtcg tggtcagaaa 60
 acccgctgta aaaacacc 78

<210> 99
 <211> 76
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:
 oligonucleotide

<400> 99
 gggcccaagc ttaagagtgt accaccattg gcagaaagtg agcagagggtg tttttacgac 60
 gggttttctg accacg 76

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<210> 100
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 100
gccacataca tttgtcgacc gtt

23

<210> 101
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 101
gggccaagc ttaagagtg

19

<210> 102
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 102
gccacataca tttgtcgacc gtt

23

<210> 103
<211> 90
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 103
ctgcagggtg acgttcgttg gcgtaaactg ttctccttca ccaaatactt cctgaaaatc 60
gaaaaaaacg gtaaagtttc tggtagcaag 90

<210> 104
<211> 90
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

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<400> 104
agctttaaca gcaacaacac cgatttcaac ggaggtgatt tccaggatgg agtacgggca 60
gttttctttc ttggtaccag aaactttacc 90

<210> 105
<211> 90
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 105
ggtgttggtg ctgttaaagc tatcaactcc aactactacc tggctatgaa caagaaaggc 60
aaactgtacg gttccaaaga atttaacaac 90

<210> 106
<211> 100
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 106
gtcgaccgtt gtgctgccag ttgaaggaag cgtaggtggt gtaaccgttt tcttcgatac 60
gttctttcag tttacagtcg ttgttaaatt ctttgaacc 100

<210> 107
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 107
gcggcgtcga ccgttggtgct gccag 25

<210> 108
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide

<400> 108
gcggcctgca gggtgacgtt cgttgg 26

<210> 109
<211> 36
<212> DNA

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<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:
oligonucleotide

<400> 109

ccggcggatc ccatatgtct tacaaccacc tgcagg

36

<210> 110

<211> 34

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:
oligonucleotide

<400> 110

cgcgcatat cttattaaga gtgtaccacc attg

34

<210> 111

<211> 426

<212> DNA

<213> Homo sapiens

<400> 111

atgtcttaca	accacctgca	gggtgacgtt	cggtggcgta	aactgttctc	cttcacaaaa	60
tacttctga	aaatcgaaaa	aaacggtaaa	gtttctggta	ccaagaaaga	aaactgcccg	120
tactccatcc	tggaaatcac	ctccggtgaa	atcgggtgtg	ttgctgttaa	agctatcaac	180
tccaactact	acctggctat	gaacaagaaa	ggtaaactgt	acggttccaa	agaatttaac	240
aacgactgta	aactgaaaga	acgtatcgaa	gaaaacgggt	acaacaccta	cgcttccttc	300
aactggcagc	acaacggctg	acaaatgtat	gtggcactga	acggtaaagg	tgctccacgt	360
cgtggtcaga	aaaccgcgtg	taaaaacacc	tctgctcact	ttctgccaat	ggtggtacac	420
tcttaa						426

<210> 112

<211> 141

<212> PRT

<213> Homo sapiens

<400> 112

Met	Ser	Tyr	Asn	His	Leu	Gln	Gly	Asp	Val	Arg	Trp	Arg	Lys	Leu	Phe
1				5					10					15	
Ser	Phe	Thr	Lys	Tyr	Phe	Leu	Lys	Ile	Glu	Lys	Asn	Gly	Lys	Val	Ser
		20						25					30		
Gly	Thr	Lys	Lys	Glu	Asn	Cys	Pro	Tyr	Ser	Ile	Leu	Glu	Ile	Thr	Ser
		35					40					45			
Val	Glu	Ile	Gly	Val	Val	Ala	Val	Lys	Ala	Ile	Asn	Ser	Asn	Tyr	Tyr
	50					55					60				
Leu	Ala	Met	Asn	Lys	Lys	Gly	Lys	Leu	Tyr	Gly	Ser	Lys	Glu	Phe	Asn
65				70				75							80
Asn	Asp	Cys	Lys	Leu	Lys	Glu	Arg	Ile	Glu	Glu	Asn	Gly	Tyr	Asn	Thr
			85					90						95	

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Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
 100 105 110

Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys
 115 120 125

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
 130 135 140

<210> 113
 <211> 28
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:
 oligonucleotide

<400> 113
 cgcgccatg gctctgggtc aggacatg 28

<210> 114
 <211> 28
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:
 oligonucleotide

<400> 114
 gggcccaagc ttatgagtgt accaccat 28

<210> 115
 <211> 516
 <212> DNA
 <213> Homo sapiens

<400> 115
 atggctctgg gtcaagatat ggtttctcog gaagctacca actcttcctc ttctcttttc 60
 tcttccccgt cttccgctgg tcgtcacgtt cgttcttaca accacctgca ggggtgacgtt 120
 cgttggcgta aactgttctc ttccacaaa tacttcctga aaatcgaaaa aaacggtaaa 180
 gtttctggga ccaagaagga gaactgcccg tacagcatcc tggagataac atcagtagaa 240
 atcggagtgt ttgccgtcaa agccattaac agcaactatt acttagccat gaacaagaag 300
 gggaaactct atggctcaa agaatttaac aatgactgta agctgaagga gaggatagag 360
 gaaaatggat acaataccta tgcatactt aactggcagc ataatgggag gcaaagtgtat 420
 gtggcattga atggaaaagg agctccaagg agaggacaga aaacacgaag gaaaaacacc 480
 tctgctcact ttcttccaat ggtggtacac tcataa 516

<210> 116
 <211> 171
 <212> PRT
 <213> Homo sapiens

<400> 116
 Met Ala Leu Gly Gln Asp Met Val Ser Pro Glu Ala Thr Asn Ser Ser
 1 5 10 15

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Ser	Ser	Ser	Phe 20	Ser	Ser	Pro	Ser	Ser	Ala	Gly	Arg	His	Val 30	Arg	Ser
Tyr	Asn	His 35	Leu	Gln	Gly	Asp	Val 40	Arg	Trp	Arg	Lys	Leu 45	Phe	Ser	Phe
Thr	Lys 50	Tyr	Phe	Leu	Lys	Ile 55	Glu	Lys	Asn	Gly	Lys 60	Val	Ser	Gly	Thr
Lys 65	Lys	Glu	Asn	Cys	Pro 70	Tyr	Ser	Ile	Leu	Glu 75	Ile	Thr	Ser	Val	Glu 80
Ile	Gly	Val	Val	Ala 85	Val	Lys	Ala	Ile	Asn 90	Ser	Asn	Tyr	Tyr	Leu 95	Ala
Met	Asn	Lys	Lys 100	Gly	Lys	Leu	Tyr	Gly 105	Ser	Lys	Glu	Phe	Asn 110	Asn	Asp
Cys	Lys	Leu 115	Lys	Glu	Arg	Ile	Glu 120	Glu	Asn	Gly	Tyr	Asn 125	Thr	Tyr	Ala
Ser	Phe 130	Asn	Trp	Gln	His	Asn 135	Gly	Arg	Gln	Met	Tyr 140	Val	Ala	Leu	Asn
Gly 145	Lys	Gly	Ala	Pro	Arg 150	Arg	Gly	Gln	Lys	Thr 155	Arg	Arg	Lys	Asn	Thr 160
Ser	Ala	His	Phe	Leu 165	Pro	Met	Val	Val	His 170	Ser					

```
<210> 117
<211> 32
<212> DNA
<213> Artificial Sequence
```

<220>
<223> Description of Artificial Sequence: primer

<400> 117
gcggcacatg tcttacaacc acctgcaggg tg 32

```
<210> 118
<211> 75
<212> DNA
<213> Artificial Sequence
```

<220>
<223> Description of Artificial Sequence: primer

```
<400> 118
ctgccccagc ttttatgagt gtaccaccat tggaagaaag tgagcagagg tgtttttttc 60
tcgtgttttc tgtcc                                     75
```

```
<210> 119
<211> 426
<212> DNA
<213> Homo sapiens
```

<400> 119

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```

atgtcttaca accacctgca gggtgacgtt cgttggcgta aactgttctc tttcaccaaa 60
tacttcctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcattcattt 300
aactggcagc ataatgggag gcaaattgtat gtggcattga atggaaaagg agctccaagg 360
agaggacaga aaacacgaga aaaaaacacc tctgctcact ttcttccaat ggtggtacac 420
tcatag                                         426

```

<210> 120

<211> 141

<212> PRT

<213> Homo sapiens

<400> 120

```

Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
  1                      5                      10                      15

```

```

Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
          20                      25                      30

```

```

Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
      35                      40                      45

```

```

Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
      50                      55                      60

```

```

Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
      65                      70                      75                      80

```

```

Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
          85                      90                      95

```

```

Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
          100                      105                      110

```

```

Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Glu Lys
      115                      120                      125

```

```

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
      130                      135                      140

```

<210> 121

<211> 32

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 121

gcggcacatg tcttacaacc acctgcaggg tg

32

<210> 122

<211> 75

<212> DNA

<213> Artificial Sequence

<220>

-50-

<223> Description of Artificial Sequence: primer

<400> 122

ctgcccagc ttttatgagt gtaccacccat tggaagaaag tgagcagagg tgtttttctg 60
 tcgtgttttc tgtcc 75

<210> 123

<211> 426

<212> DNA

<213> Homo sapiens

<400> 123

atgtcttaca accacctgca gggtgacgtt cgttggcgta aactgttctc tttcaccaaa 60
 tacttctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
 tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
 agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
 aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcattcattt 300
 aactggcagc ataatgggag gcaaattgat gtggcattga atggaaaagg agctccaagg 360
 agaggacaga aaacacgaca gaaaaacacc tctgctcact ttcttccaat ggtggtacac 420
 tcatag 426

<210> 124

<211> 141

<212> PRT

<213> Homo sapiens

<400> 124

Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
 1 5 10 15
 Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
 20 25 30
 Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
 35 40 45
 Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
 50 55 60
 Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
 65 70 75 80
 Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
 85 90 95
 Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
 100 105 110
 Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Gln Lys
 115 120 125
 Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
 130 135 140

<210> 125

<211> 32

<212> DNA

<213> Artificial Sequence

-51-

<220>

<223> Description of Artificial Sequence: primer

<400> 125

gcggcacatg tcttacaacc acctgcaggg tg

32

<210> 126

<211> 84

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 126

ctgcccgaagc ttttatgagt gtaccaccat tggaagaaag tgagcagagg tgtttttccct 60
tcgtgtttcc tgcctctcc ttgg 84

<210> 127

<211> 426

<212> DNA

<213> Homo sapiens

<400> 127

atgtcttaca accacctgca ggggtgacgtt cggtggcgta aactgttctc tttcaccaaa 60
tacttcctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcatacatt 300
aactggcagc ataatgggag gcaaatgtat gtggcattga atggaaaagg agctccaagg 360
agaggacagg aaacacgaag gaaaaacacc tctgctcact ttcttccaat ggtggtacac 420
tcatag 426

<210> 128

<211> 141

<212> PRT

<213> Homo sapiens

<400> 128

Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
1 5 10 15Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
20 25 30Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
35 40 45Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
50 55 60Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
65 70 75 80Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
85 90 95Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
100 105 110

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Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Glu Thr Arg Arg Lys
 115 120 125

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
 130 135 140

<210> 129

<211> 32

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 129

gcggcacatg tcttacaacc acctgcaggg tg

32

<210> 130

<211> 84

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 130

ctgccaagc ttttatgagt gtaccacat tggaagaaag tgagcagagg tgtttttcct 60
 tcgtgtctgc tgcctctcc ttgg 84

<210> 131

<211> 426

<212> DNA

<213> Homo sapiens

<400> 131

atgtcttaca accacctgca gggtagcgtt cgttggcgta aactgttctc tttcaccaaa 60
 tacttcctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
 tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
 agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
 aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcattcattt 300
 aactggcagc ataatgggag gcaaatgtat gtggcattga atggaaaagg agctccaagg 360
 agaggacagc agacacgaag gaaaaacacc tctgtctact ttcttccaat ggtggtacac 420
 tcatag 426

<210> 132

<211> 141

<212> PRT

<213> Homo sapiens

<400> 132

Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
 1 5 10 15

Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
 20 25 30

Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
 35 40 45

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Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
 50 55 60

Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
 65 70 75 80

Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
 85 90 95

Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
 100 105 110

Leu Asn Gly Lys Gly Ala Pro Arg Arg Gly Gln Gln Thr Arg Arg Lys
 115 120 125

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
 130 135 140

<210> 133

<211> 32

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 133

gcggcacatg tcttacaacc acctgcaggg tg

32

<210> 134

<211> 93

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 134

ctgcccgaagc ttttatgagt gtaccacat tggaagaaag tgagcagagg tgtttttctt 60
 tcgtgttttc tgccttccc ttggagctcc ttt 93

<210> 135

<211> 426

<212> DNA

<213> Homo sapiens

<400> 135

atgtcttaca accacctgca ggggtgacgtt cgttggcgta aactgttctc tttcaccaaa 60
 tacttcttga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
 tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
 agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
 aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcattcattt 300
 aactggcagc ataatgggag gcaaatgtat gtggcattga atggaaaagg agctccaagg 360
 gaaggacaga aaacacgaag gaaaaacacc tctgtctact ttcttccaat ggtggtacac 420
 tcatag 426

<210> 136

<211> 140

-54-

<212> PRT

<213> Homo sapiens

<400> 136

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Met Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe Ser
 1           5           10           15
Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser Gly
           20           25           30
Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser Val
           35           40           45
Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr Leu
 50           55           60
Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn Asn
 65           70           75           80
Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr Tyr
           85           90           95
Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala Leu
           100          105          110
Asn Gly Lys Gly Ala Pro Arg Glu Gly Gln Lys Thr Arg Arg Lys Asn
 115          120          125
Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
 130          135          140

```

<210> 137

<211> 32

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 137

gcggcacatg tcttacaacc acctgcaggg tg

32

<210> 138

<211> 93

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 138

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ctgcccgaagc ttttatgagt gtaccaccat tggaagaaag tgagcagagg tgtttttcct 60
tcgtgttttc tgtccctgcc ttggagctcc ttt 93

```

<210> 139

<211> 426

<212> DNA

<213> Homo sapiens

-55-

<400> 139
 atgtcttaca accacctgca ggggtgacgtt cgttgggcgta aactgttctc tttcaccaaa 60
 tactttcctga aaatcgaaaa aaacggtaaa gtttctggga ccaagaagga gaactgcccg 120
 tacagcatcc tggagataac atcagtagaa atcggagttg ttgccgtcaa agccattaac 180
 agcaactatt acttagccat gaacaagaag gggaaactct atggctcaaa agaatttaac 240
 aatgactgta agctgaagga gaggatagag gaaaatggat acaataccta tgcattcatt 300
 aactggcagc ataatgggag gcaaatgtat gtggcattga atggaaaagg agctccaagg 360
 cagggacaga aaacacgaag gaaaaacacc tctgctcact ttcttccaat ggtggtacac 420
 tcatag 426

<210> 140
 <211> 141
 <212> PRT
 <213> Homo sapiens

<400> 140
 Met Ser Tyr Asn His Leu Gln Gly Asp Val Arg Trp Arg Lys Leu Phe
 1 5 10 15
 Ser Phe Thr Lys Tyr Phe Leu Lys Ile Glu Lys Asn Gly Lys Val Ser
 20 25 30
 Gly Thr Lys Lys Glu Asn Cys Pro Tyr Ser Ile Leu Glu Ile Thr Ser
 35 40 45
 Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
 50 55 60
 Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
 65 70 75 80
 Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
 85 90 95
 Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
 100 105 110
 Leu Asn Gly Lys Gly Ala Pro Arg Gln Gly Gln Lys Thr Arg Arg Lys
 115 120 125
 Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
 130 135 140

<210> 141
 <211> 32
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

<400> 141
 gcggcacatg tcttacaacc acctgcaggg tg 32

<210> 142
 <211> 21
 <212> DNA
 <213> Artificial Sequence

-56-

<220>

<223> Description of Artificial Sequence: primer

<400> 142

ttgaatggag aaggagctcc a

21

<210> 143

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 143

tggagctcct tctccattca a

21

<210> 144

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 144

ctgcccgaagc ttttatgagt gtaccacat tgg

33

<210> 145

<211> 426

<212> DNA

<213> Homo sapiens

<400> 145

atgtcttaca	accacctgca	gggtgacgtt	cgttggcgta	aactgttctc	tttcaccaa	60
tacttcctga	aaatcgaaaa	aaacggtaaa	gtttctggga	ccaagaagga	gaactgccc	120
tacagcatcc	tggagataac	atcagtagaa	atcggagttg	ttgccgtcaa	agccattaac	180
agcaactatt	acttagccat	gaacaagaag	gggaaactct	atggctcaa	agaatttaac	240
aatgactgta	agctgaagga	gaggatagag	gaaaatggat	acaataccta	tgcatcattt	300
aactggcagc	ataatgggag	gcaaattgtat	gtggcattga	atggagaagg	agctccaagg	360
agaggacaga	aaacacgaag	gaaaaacacc	tctgctcact	ttcttccaat	ggtggtaçac	420
tcatag						426

<210> 146

<211> 141

<212> PRT

<213> Homo sapiens

<400> 146

Met	Ser	Tyr	Asn	His	Leu	Gln	Gly	Asp	Val	Arg	Trp	Arg	Lys	Leu	Phe
1				5					10					15	

Ser	Phe	Thr	Lys	Tyr	Phe	Leu	Lys	Ile	Glu	Lys	Asn	Gly	Lys	Val	Ser
			20					25					30		

Gly	Thr	Lys	Lys	Glu	Asn	Cys	Pro	Tyr	Ser	Ile	Leu	Glu	Ile	Thr	Ser
		35					40					45			

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Val Glu Ile Gly Val Val Ala Val Lys Ala Ile Asn Ser Asn Tyr Tyr
 50 55 60

Leu Ala Met Asn Lys Lys Gly Lys Leu Tyr Gly Ser Lys Glu Phe Asn
 65 70 75 80

Asn Asp Cys Lys Leu Lys Glu Arg Ile Glu Glu Asn Gly Tyr Asn Thr
 85 90 95

Tyr Ala Ser Phe Asn Trp Gln His Asn Gly Arg Gln Met Tyr Val Ala
 100 105 110

Leu Asn Gly Glu Gly Ala Pro Arg Arg Gly Gln Lys Thr Arg Arg Lys
 115 120 125

Asn Thr Ser Ala His Phe Leu Pro Met Val Val His Ser
 130 135 140

<210> 147

<211> 3974

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: pHE4-5 vector

<400> 147

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ggtacctaag tgagtagggc gtccgatcga cggacgcctt ttttttgaat tcgtaatcat 60
ggtcatagct gtttcctgtg tgaaattgtt atccgctcac aattccacac aacatacgag 120
ccggaagcat aaagtgtaaa gcctgggggtg cctaagtgtg gagctaactc acattaattg 180
cggtgcgctc actgcccgct ttccagtcgg gaaacctgtc gtgccagctg cattaatgaa 240
tcggccaacg cgcggggaga ggcggtttgc gtattgggcg ctcttcgcgt tcctcgctca 300
ctgactcgct gcgctcggtc gttcggtgct ggcgagcggg atcagctcac tcaaaggcgg 360
taatacgggt atccacagaa tcaggggata acgcaggaaa gaacatgtga gcaaaaggcc 420
agcaaaaggc caggaaccgt aaaaaggccg cggtgctggc gtttttccat aggctccgcc 480
cccctgacga gcatcacaaa aatcgacgct caagtcagag gtggcgaaac ccgacaggac 540
tataaagata ccaggcggtt cccctgggaa gtcctctcgt gcgctctcct gttccgacct 600
tgccgcttac cggatacctg tccgcctttc tcccttcggg aagcgtggcg ctttctcata 660
gctcacgctg taggtatctc agttcggtgt aggtcggtcg ctccaagctg ggctgtgtgt 720
ctgacgctca gtggaacgaa aactcacggt aagggtttt ggtcatgaga ttatcgtcga 780
acccggttaag acacgaacta tcgccactgg cagcagccac tggtaacagg attagcagag 840
cgaggtatgt aggcggtgct acagagttct tgaagtgtgt gcctaactac ggctacacta 900
gaagaacagt atttggtatc tgcgctctgc tgaagccagt taccttcgga aaaagagttg 960
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agcggcgtcg aagcctgtaa agcggcggtg cacaatcttc tcgcgcaacg cgtcagtggt 1620
ctgatcatta actatccgct ggatgaccag gatgccattg ctgtggaagc tgcctgcact 1680
aatgttcggc cgttatttct tgatgtctct gaccagacac ccatcaacag tattattttc 1740
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cataaatatc tcaactgcaa tcaaattcag ccgatagcgg aacgggaagg cgactggagt 1920
gccatgtccg gttttcaaca aaccatgcaa atgctgaatg agggcatcgt tcccactgcg 1980
atgctgggtg ccaacgatca gatggcgctg ggcgcaatgc gcgccattac cgagtccggg 2040

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ctgcgcgttg gtgcggatat ctcggttagtg ggatacgacg ataccgaaga cagctcatgt 2100
tatatccccg cgtaaacac catcaaacag gattttcgcc tgctggggca aaccagcgtg 2160
gaccgcttg tgcaactctc tcagggccag gcggtgaagg gcaatcagct gttgcccgtc 2220
tcaactggtga aaagaaaaac caccctggcg cccaatacgc aaaccgcctc tcccgcgcg 2280
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ggcggcggtg gaatcgaaat ctctgatgg caggttggc gtcgcttggg cggtcatttc 2700
gaaccccaga gtcccgtca gaagaactcg tcaagaaggc gatagaaggc gatgcgctgc 2760
gaatcgggag cggcgatacc gtaaagcac aggaagcggc cagcccattc gccgccaagc 2820
tcttcagcaa tatcacgggt agccaacgct atgtcctgat agcgtccgc cacaccagc 2880
cggccacagt cgatgaatcc agaaaagcgg ccattttcca ccatgatatt cggcaagcag 2940
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aacagttcgg ctggcgcgag cccctgatgc tcttcgtcca gatcatcctg atcgacaaga 3060
ccggttcca tccgagtacg tgctcgctcg atgcgatgtt tcgcttggg gtcgaatggg 3120
caggtagccg gatcaagcgt atgcagccgc cgcattgcat cagccatgat ggatactttc 3180
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gccagccacg atagccgcgc tgcctcgtcc tgcagttcat tcagggcacc ggacaggtcg 3360
gtcttgacaa aaagaaccgg gcgcccctgc gctgacagcc ggaacacggc ggcacagag 3420
cagccgattg tctgttgtgc ccagtcatag ccgaatagcc tctccacca agcggccgga 3480
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ttgcagggct tcccaacctt accagagggc gcccagctg gcaattccg ttcgcttgc 3660
gtccataaaa ccgcccagtc tagctatcgc catgtaagcc cactgcaagc tacctgcttt 3720
ctctttgcgc ttgcgttttc cctgttccag atagcccagt agctgacatt catccgggg 3780
cagcaccgtt tctgcggact ggctttctac gtgttccgct tcctttagca gcccttgcgc 3840
cctgagtgtc tgccgagcg tgaagcttaa aaaactgcaa aaaatagttt gacttgtgag 3900
cggataacaa ttaagatgta cccaattgtg agcggataac aatttcacac attaaagagg 3960
agaaattaca tatg 3974

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<210> 148
 <211> 112
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: pHE4-5
 promoter sequence

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<400> 148
aagcttaaaa aactgcaaaa aatagtttga cttgtgagcg gataacaatt aagatgtacc 60
caattgtgag cggataacaa ttccacacat taaagaggag aaattacata tg 112

```

<210> 149
 <211> 106
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

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<400> 149
gagcgcggat ccgccaccat gaaggtctcc gtggctgccc tctcctgcct catgcttgtt 60
actgcccttg gatcgcaggc cagctacaat caccttcaag gagatg 106

```

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<210> 150
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 150
gagcgcggat ccctatgagt gtaccacat tggaag 36

<210> 151
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 151
ccggccatat gcgtaaactg ttctctttca cc 32

<210> 152
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 152
ccggcggtag cttattatga gtgtaccacc attgg 35

<210> 153
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 153
gatcgccata tggctggtag tcacgttcgt tc 32

<210> 154
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 154
gatcgcggta ccttattatg agtgtaccac cattggaag 39

<210> 155
<211> 32

-60-

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 155
gatcgccata tggctgggtcg tcacgttcgt tc 32

<210> 156
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 156
gatcgcggtta ccttattatg agtgtaccac cattggaag 39

<210> 157
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 157
gatcgccata tggctgggtcg tcacgttcgt tc 32

<210> 158
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 158
gatcgcggtta ccttattatg agtgtaccac cattggaag 39

<210> 159
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 159
gatcgccata tggctgggtcg tcacgttcgt tc 32

<210> 160
<211> 39
<212> DNA
<213> Artificial Sequence

-61-

<220>
<223> Description of Artificial Sequence: primer

<400> 160
gatcgcggta ccttattatg agtgtaccac cattggaag 39

<210> 161
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 161
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<210> 162
<211> 40
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 162
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-63-

<210> 171
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 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

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<210> 172
 <211> 39
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: primer

<400> 172
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<210> 173
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 <212> DNA
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 accaagaagg agaactgcc gtacagcatc ctggagataa catcagtaga aatcggagtt 180
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 tacaatacct atgcatcatt taactggcag cataatggga ggcaaagtga tgtggcattg 360
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<220>
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<400> 175

-64-

ctagtctcta gattattatg agtgtacaac catcggcagg aagtgag

47

<210> 176

<211> 447

<212> DNA

<213> Escherichia coli

<400> 176

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